

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
7 March 2002 (07.03.2002)

PCT

(10) International Publication Number
WO 02/18383 A2

(51) International Patent Classification⁷: C07D 471/04,
A61K 31/435, A61P 35/00, C07D 519/00, 495/04 //
(C07D 471/04, 221:00, 221:00) (C07D 471/04, 231:00,
221:00) (C07D 471/04, 235:00, 221:00) (C07D 495/04,
333:00, 221:00) (C07D 519/00, 471:00, 471:00)

MACHAJEWSKI, Tim [US/US]; 2514 Norwalk Court,
Martinez, CA 94553 (US). SHAFER, Cynthia [US/US];
4868 El Grande Place, El Sobrante, CA 94803 (US).
WERNETTE-HAMMOND, Mary-Ellen [US/US];
17893 Center Street, Castro Valley, CA 94546 (US).
HARRIS, Alex [US/US]; 14 MacPherson Place, Danville,
CA 94526 (US).

(21) International Application Number: PCT/US01/41942

(22) International Filing Date: 30 August 2001 (30.08.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/231,829 1 September 2000 (01.09.2000) US

(71) Applicant (for all designated States except US): CHI-
RON CORPORATION [US/US]; 4560 Horton Street,
Emeryville, CA 94608-2916 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): RENHOWE, Paul
[US/US]; 262 Stetson Drive, Danville, CA 94506 (US).

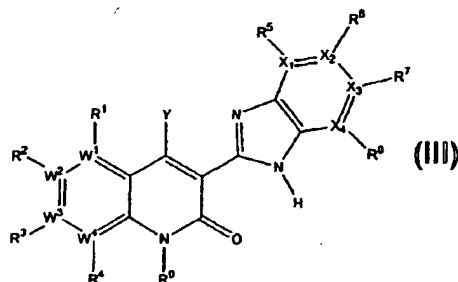
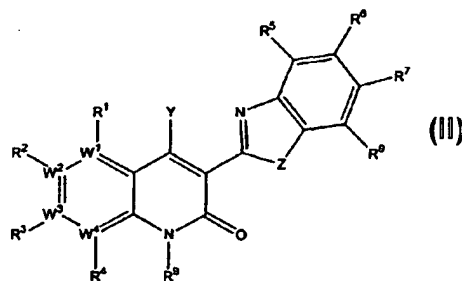
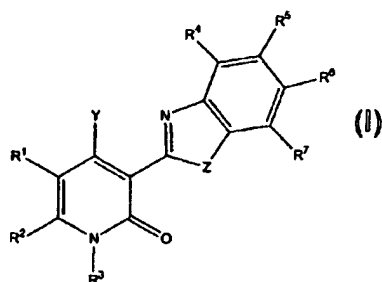
(74) Agent: FRIEDRICHSEN, Bernard; Foley & Lardner,
150 East Gilman Street, P.O. Box 1497, Madison, WI
53701-1497 (US).

(81) Designated States (national): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI,
SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU,
ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian

[Continued on next page]

(54) Title: HETEROCYCLIC COMPOUNDS



(57) Abstract: Organic compounds having the structural formulas I, II, and III are provided where the variable have the values described herein and R⁷ and R² in structure I join together to form a 5 to 7 membered substituted or unsubstituted ring including at least one O, N, or S atom, and Z is an O, S, NH or NR group in structures I and II. Formula I, II, III: Pharmaceutical formulation include the organic compound or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier. A method of treating a patient includes administering a pharmaceutical formulation according to the invention to a patient in need thereof.

WO 02/18383 A2

patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

Published:

— *without international search report and to be republished upon receipt of that report*

WO 02/18383

PCT/US01/41942

HETEROCYCLIC COMPOUNDS

FIELD OF THE INVENTION

This invention pertains generally to treating diseases characterized by angiogenesis including cancer. More specifically, the invention described herein pertains to treating diseases characterized by activity of vascular endothelial growth factor receptor tyrosine kinases. The present invention provides small molecule inhibitors of vascular endothelial growth factor receptor tyrosine kinase, pharmaceutical formulations containing such inhibitors, methods of treating patients with such pharmaceutical formulations, and to methods of preparing such pharmaceutical formulations and inhibitors.

BACKGROUND OF THE INVENTION

Capillaries reach into almost all tissues of the human body and supply tissues with oxygen and nutrients as well as removing waste products. Under typical conditions, the endothelial cells lining the capillaries do not divide, and capillaries, therefore, do not normally increase in number or size in a human adult. Under certain normal conditions, however, such as when a tissue is damaged, or during certain parts of the menstrual cycle, the capillaries begin to proliferate rapidly. This process of forming new capillaries from pre-existing blood vessels is known as angiogenesis or neovascularization. See Folkman, J. Scientific American 275, 150-154 (1996). Angiogenesis during wound healing is an example of pathophysiological neovascularization during adult life. During wound healing, the additional capillaries provide a supply of oxygen and nutrients, promote granulation tissue, and aid in waste removal. After termination of the healing process, the capillaries normally regress. Lymboussaki, A. "Vascular Endothelial Growth Factors and their Receptors in Embryos, Adults, and in Tumors" Academic

WO 02/18383

PCT/US01/41942

-2-

Dissertation, University of Helsinki, Molecular/Cancer Biology Laboratory and Department of Pathology, Haartman Institute, (1999).

Angiogenesis also plays an important role in the growth of cancer cells. It is known that once a nest of cancer cells reaches a certain size, roughly 1 to 2 mm in
5 diameter, the cancer cells must develop a blood supply in order for the tumor to grow larger as diffusion will not be sufficient to supply the cancer cells with enough oxygen and nutrients. Thus, inhibition of angiogenesis is expected to retard or halt the growth of cancer cells.

Receptor tyrosine kinases (RTKs) are transmembrane polypeptides
10 that regulate developmental cell growth and differentiation and remodeling and regeneration of adult tissues. Mustonen, T. et al., J. Cell Biology 129, 895-898 (1995); van der Geer, P. et al. Ann Rev. Cell Biol. 10, 251-337 (1994). Polypeptide ligands known as growth factors, or cytokines, are known to activate RTKs. Signaling of RTKs involves ligand binding and a shift in conformation in
15 the external domain of the receptor resulting in its dimerization. Lymboussaki, A. "Vascular Endothelial Growth Factors and their Receptors in Embryos, Adults, and in Tumors" Academic Dissertation, University of Helsinki, Molecular/Cancer Biology Laboratory and Department of Pathology, Haartman Institute, (1999); Ullrich, A. et al., Cell 61, 203-212 (1990). Binding of the ligand to the RTK
20 results in receptor trans-phosphorylation at specific tyrosine residues and subsequent activation of the catalytic domains for the phosphorylation of cytoplasmic substrates. Id.

Two subfamilies of RTKs are specific to the vascular endothelium. These include the vascular endothelial growth factor (VEGF) subfamily and the Tie
25 receptor subfamily. Class III RTKs include VEGFR-1, VEGFR-2, and VEGFR-3. Shibuya, M. et al., Oncogene 5, 519-525 (1990); Terman, B. et al., Oncogene 6, 1677-1683 (1991); Aprelikova, O. et al., Cancer Res. 52, 746-748 (1992).

WO 02/18383

PCT/US01/41942

-3-

Members of the VEGF subfamily have been described as being able to induce vascular permeability and endothelial cell proliferation and further identified as a major inducer of angiogenesis and vasculogenesis. Ferrara, N. et al., *Endocrinol. Rev.* 18, 4-25 (1997). VEGF is known to specifically bind to

5 RTKs including VEGFR-1 and VEGFR-2. DeVries, C. et al., *Science* 255, 989-991 (1992); Quinn, T. et al., *Proc. Natl. Acad. Sci.* 90, 7533-7537 (1993). VEGF stimulates the migration and proliferation of endothelial cells and induces angiogenesis both in vitro and in vivo. Connolly, D. et al., *J. Biol. Chem.* 264, 20017-20024 (1989); Connolly, D. et al., *J. Clin. Invest.* 84, 1470-1478 (1989);

10 Ferrara, N. et al., *Endocrino. Rew.* 18, 4-25 (1997); Leung, D. et al., *Science* 246, 1306-1309 (1989); Plouet, J. et al., *EMBO J* 8, 3801-3806 (1989).

Because angiogenesis is known to be critical to the growth of cancer and to be controlled by VEGF and VEGF-RTK, substantial efforts have been undertaken to develop therapeutics that are antagonists of VEGF-RTK to thereby

15 inhibit or retard angiogenesis, and hopefully interfere or stop tumor proliferation.

A wide variety of chemical compounds and compositions have been reported as having activity against one of more the VEGF-RTKs. Examples include quinoline derivatives such as described in WO 98/13350, aminonicotinamide derivatives (see, *e.g.*, WO 01/55114), antisense compounds (see, *e.g.*, WO

20 01/52904), peptidomimetics (see, *e.g.*, WO 01/52875), quinazoline derivatives (see, *e.g.*, U.S. Patent No. 6,258,951) monoclonal antibodies (see, *e.g.*, EP 1 086 705 A1), various 5,10,15,20-tetraaryl-porphyrins and 5,10,15-triaryl-corroles (see, *e.g.*, WO 00/27379), heterocyclic alkanesulfonic and alkane carboxylic acid derivatives (see, *e.g.*, DE19841985), oxindolylquinazoline derivatives (see, *e.g.*,

25 WO 99/10349), 1,4-diazaanthracene derivatives (see, *e.g.*, U.S. Patent No. 5,763,441), and cinnoline derivatives (see, *e.g.*, WO 97/34876), and various indazole compounds (see *e.g.*, WO 01/02369 and WO 01/02369).

Various indolyl-substituted compounds have recently been disclosed in WO 01/29025, and various benzimidazolyl compounds have recently been

WO 02/18383

PCT/US01/41942

-4-

disclosed in WO 01/28993. These compounds are reportedly capable of inhibiting, modulating, and/or regulating signal transduction of both receptor-type and non-receptor tyrosine kinases. Some of the disclosed compounds contain a quinolone fragment bonded to the indolyl or benzimidazolyl group.

5 The synthesis of 4-hydroxy quinolone and 4-hydroxy quinoline derivatives is disclosed in a number of references. For example, Ukrainets et al. have disclosed the synthesis of 3-(Benzimidazol-2-yl)-4-hydroxy-2-oxo-1,2-dihydroquinoline. Ukrainets, I. et al., Tet. Lett. 42, 7747-7748 (1995); Ukrainets, I. et al., Khimiya Geterotsiklicheskikh Soedinii, 2, 239-241(1992). Ukrainets has
10 also disclosed the synthesis, anticonvulsive and antithyroid activity of other 4-hydroxy quinolones and thio analogs such as 1H-2-oxo-3-(2-benzimidazolyl)-4-hydroxyquinoline. Ukrainets, I. et al., Khimiya Geterotsiklicheskikh Soedinii, 1, 105-108 (1993); Ukrainets, I. et al., Khimiya Geterotsiklicheskikh Soedinii, 8, 1105-1108 (1993); Ukrainets, I. et al., Chem. Heterocyclic Comp. 33, 600-604,
15 (1997).

 The synthesis of various quinoline derivatives is disclosed in WO 97/48694. These compounds are disclosed as capable of binding to nuclear hormone receptors and being useful for stimulating osteoblast proliferation and bone growth. The compounds are also disclosed as being useful in the treatment or
20 prevention of diseases associated with nuclear hormone receptor families.

 Various quinoline derivatives in which the benzene ring of the quinolone is substituted with a sulfur group are disclosed in WO 92/18483. These compounds are disclosed as being useful in pharmaceutical formulations and as medicaments.

25 Quinolone and coumarin derivatives have been disclosed as having use in a variety of applications unrelated to medicine and pharmaceutical formulations. References that describe the preparation of quinolone derivatives for use in photopolymerizable compositions or for luminescent properties include: U.S.

WO 02/18383

PCT/US01/41942

-5-

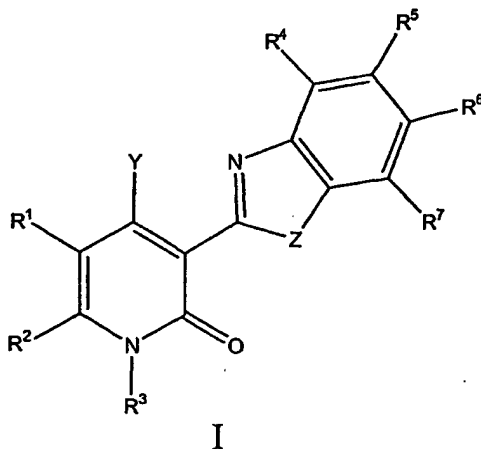
Patent No. 5,801,212 issued to Okamoto et al.; JP 8-29973; JP 7-43896; JP 6-9952; JP 63-258903; EP 797376; and DE 23 63 459.

Despite the exploration of a variety of chemistries to provide VEGF-RTK-antagonist therapies, a continuing need exists for compounds that inhibit the proliferation of capillaries, inhibit the growth of tumors, and/or inhibit vascular endothelial growth factor receptor tyrosine kinase and pharmaceutical formulations that contain such compounds. A need also exists for methods for administering such compounds and pharmaceutical formulations to patients in need thereof.

SUMMARY OF THE INVENTION

10 The present invention provides compounds, pharmaceutical formulations including the compounds, methods of preparing the pharmaceutical formulations, and methods of treating patients with the pharmaceutical formulations and compounds.

The present invention provides compounds having the structure I.
15 The invention also provides tautomers of the compounds, pharmaceutically acceptable salts of the compounds, and pharmaceutically acceptable salts of the tautomers. Structure I has the following formula:



WO 02/18383

PCT/US01/41942

-6-

where:

Y is selected from -OH, -OR⁸ groups, -SH, -SR⁹ groups, -NR¹⁰R¹¹ groups, -CN, -C(=O)-R¹² groups, substituted or unsubstituted alkyl groups, substituted or unsubstituted alkenyl groups, substituted or unsubstituted alkynyl groups, substituted or unsubstituted aralkyl groups, substituted or unsubstituted heterocyclalkyl groups, substituted or unsubstituted alkylaminoalkyl groups, substituted or unsubstituted dialkylaminoalkyl groups, substituted or unsubstituted arylaminoalkyl groups, substituted or unsubstituted diarylaminoalkyl groups, substituted or unsubstituted (alkyl)(aryl)aminoalkyl groups, substituted or unsubstituted heterocyclaminoalkyl groups, substituted and unsubstituted diheterocyclaminoalkyl groups, substituted and unsubstituted (alkyl)(heterocycl)aminoalkyl groups, substituted and unsubstituted (aryl)(heterocycl)aminoalkyl groups, substituted or unsubstituted heterocycl groups, substituted or unsubstituted aryl groups, substituted or unsubstituted hydroxyalkyl groups, substituted or unsubstituted alkoxyalkyl groups, substituted or unsubstituted aryloxyalkyl groups, or substituted or unsubstituted heterocycloxyalkyl groups;

Z is O, S, or a NR¹³ group;

R¹ and R² join to form a 5 to 7 membered substituted or unsubstituted ring including at least one O, N, or S atom;

R³ and R¹³ may be the same or different and are selected from H, -OH, substituted or unsubstituted alkoxy groups, substituted or unsubstituted aryloxy groups, -NH₂, substituted or unsubstituted alkylamino groups, substituted or unsubstituted arylamino groups, substituted or unsubstituted dialkylamino groups, substituted or unsubstituted diarylamino groups, substituted or unsubstituted (alkyl)(aryl)amino groups, substituted and unsubstituted heterocyclamino groups, substituted and unsubstituted diheterocyclamino groups, substituted and unsubstituted (alkyl)(heterocycl)amino groups, substituted and unsubstituted

WO 02/18383

PCT/US01/41942

-7-

(aryl)(heterocyclyl)amino groups, substituted and unsubstituted heterocyclyloxy groups, substituted or unsubstituted alkyl groups, substituted or unsubstituted aryl groups, -C(=O)H, -C(=O)-alkyl groups, or -C(=O)-aryl groups;

- R⁴, R⁵, R⁶, and R⁷ may be the same or different and are
- 5 independently selected from H, Cl, Br, F, I, -NO₂, -CN, -OH, -OR¹⁴ groups, -NR¹⁵R¹⁶ groups, -C(=O)R¹⁷ groups, -SH, -SR¹⁸ groups, -S(=O)R¹⁹ groups, S(=O)₂R²⁰ groups, substituted or unsubstituted amidinyl groups, substituted or unsubstituted guanidinyl groups, substituted or unsubstituted primary, secondary, or tertiary alkyl groups, substituted or unsubstituted aryl groups, substituted or
- 10 unsubstituted alkenyl groups, substituted or unsubstituted alkynyl groups, substituted or unsubstituted heterocyclyl groups, substituted or unsubstituted alkylaminoalkyl groups, substituted or unsubstituted dialkylaminoalkyl groups, substituted or unsubstituted arylaminoalkyl groups, substituted or unsubstituted diarylaminoalkyl groups, substituted or unsubstituted (alkyl)(aryl)aminoalkyl
- 15 groups, substituted and unsubstituted diheterocyclylaminoalkyl groups, substituted and unsubstituted (alkyl)(heterocyclyl)aminoalkyl groups, substituted and unsubstituted (aryl)(heterocyclyl)aminoalkyl groups, substituted or unsubstituted heterocyclylalkyl groups, substituted or unsubstituted aminoalkyl groups, substituted or unsubstituted heterocyclylaminoalkyl groups, substituted or unsubstituted
- 20 hydroxyalkyl groups, substituted or unsubstituted alkoxyalkyl groups, substituted or unsubstituted aryloxyalkyl groups, or substituted or unsubstituted heterocyclyloxyalkyl groups;

- R⁸ is selected from substituted or unsubstituted alkyl groups, substituted or unsubstituted aryl groups, substituted or unsubstituted heterocyclyl
- 25 groups, substituted or unsubstituted heterocyclylalkyl groups, -C(=O)H, -C(=O)-alkyl groups, -C(=O)-aryl groups, -C(=O)O-alkyl groups, -C(=O)O-aryl groups, -C(=O)NH₂, -C(=O)NH(alkyl) groups, -C(=O)NH(aryl) groups, -C(=O)N(alkyl)₂ groups, -C(=O)N(aryl)₂ groups, -C(=O)N(alkyl)(aryl) groups, -NH₂, -NH(alkyl) groups, -NH(aryl) groups, -N(alkyl)₂ groups, -N(alkyl)(aryl)

WO 02/18383

PCT/US01/41942

-8-

groups, -N(aryl)₂ groups, -C(=O)NH(heterocyclyl) groups,
 -C(=O)N(heterocyclyl)₂ groups, -C(=O)N(alkyl)(heterocyclyl) groups, or
 -C(=O)N(aryl)(heterocyclyl) groups;

R⁹ and R¹⁸ may be the same or different and are independently
 5 selected from substituted or unsubstituted alkyl groups, or substituted or
 unsubstituted aryl groups;

R¹⁰ is selected from H, substituted or unsubstituted alkyl groups,
 substituted or unsubstituted aryl groups, or substituted or unsubstituted heterocyclyl
 groups;

10 R¹¹ is selected from H, substituted or unsubstituted alkyl groups,
 substituted or unsubstituted aryl groups, substituted or unsubstituted heterocyclyl
 groups, -OH, alkoxy groups, aryloxy groups, -NH₂, substituted or unsubstituted
 heterocyclylalkyl groups, substituted or unsubstituted aminoalkyl groups, substituted
 or unsubstituted alkylaminoalkyl groups, substituted or unsubstituted
 15 dialkylaminoalkyl groups, substituted or unsubstituted arylaminoalkyl groups,
 substituted or unsubstituted diarylaminoalkyl groups, substituted or unsubstituted
 (alkyl)(aryl)aminoalkyl groups, substituted or unsubstituted alkylamino groups,
 substituted or unsubstituted arylamino groups, substituted or unsubstituted
 dialkylamino groups, substituted or unsubstituted diarylamino groups, substituted or
 20 unsubstituted (alkyl)(aryl)amino groups, -C(=O)H, -C(=O)-alkyl groups,
 -C(=O)-aryl groups, -C(=O)O-alkyl groups, -C(=O)O-aryl groups, -C(=O)NH₂,
 -C(=O)NH(alkyl) groups, -C(=O)NH(aryl) groups, -C(=O)N(alkyl)₂ groups,
 -C(=O)N(aryl)₂ groups, -C(=O)N(alkyl)(aryl) groups, -C(=O)-heterocyclyl
 groups, -C(=O)-O-heterocyclyl groups, -C(=O)NH(heterocyclyl) groups,
 25 -C(=O)-N(heterocyclyl)₂ groups, -C(=O)-N(alkyl)(heterocyclyl) groups,
 -C(=O)-N(aryl)(heterocyclyl) groups, substituted or unsubstituted
 heterocyclylaminoalkyl groups, substituted and unsubstituted
 diheterocyclylaminoalkyl groups, substituted and unsubstituted
 (alkyl)(heterocyclyl)aminoalkyl groups, substituted and unsubstituted

WO 02/18383

PCT/US01/41942

-9-

(aryl)(heterocyclyl)aminoalkyl groups, substituted or unsubstituted hydroxyalkyl groups, substituted or unsubstituted alkoxyalkyl groups, substituted or unsubstituted aryloxyalkyl groups, or substituted or unsubstituted heterocyclyloxyalkyl groups;

R¹² is selected from H, -OH, alkoxy groups, aryloxy groups, -NH₂,
5 -NH(alkyl) groups, -NH(aryl) groups, -N(alkyl)₂ groups, -N(aryl)₂ groups,
-N(alkyl)(aryl) groups, substituted or unsubstituted alkyl groups, substituted or
unsubstituted aryl groups, -NH(heterocyclyl) groups, -N(heterocyclyl)₂ groups,
-N(alkyl)(heterocyclyl) groups, or -N(aryl)(heterocyclyl) groups;

R¹⁴ is selected from substituted or unsubstituted alkyl groups,
10 substituted or unsubstituted aryl groups, substituted or unsubstituted heterocyclyl
groups, substituted or unsubstituted heterocyclylalkyl groups, -C(=O)H,
-C(=O)-alkyl groups, -C(=O)-aryl groups, -C(=O)-heterocyclyl
groups, -C(=O)NH₂, -C(=O)NH(alkyl) groups, -C(=O)NH(aryl) groups,
-C(=O)N(alkyl)₂ groups, -C(=O)N(aryl)₂ groups, -C(=O)N(alkyl)(aryl) groups,
15 -C(=O)NH-heterocyclyl groups, -C(=O)N-(heterocyclyl)₂ groups,
-C(=O)N(alkyl)(heterocyclyl) groups, -C(=O)N(aryl)(heterocyclyl) groups,
substituted or unsubstituted aminoalkyl groups, substituted or unsubstituted
alkylaminoalkyl groups, substituted or unsubstituted dialkylaminoalkyl groups,
substituted or unsubstituted arylaminoalkyl groups, substituted or unsubstituted
20 diarylaminoalkyl groups, substituted or unsubstituted (alkyl)(aryl)aminoalkyl
groups, substituted or unsubstituted heterocyclylaminoalkyl groups, substituted or
unsubstituted diheterocyclylaminoalkyl groups, substituted or unsubstituted
(heterocyclyl)(alkyl)aminoalkyl groups, substituted or unsubstituted
(heterocyclyl)(aryl)aminoalkyl groups, substituted or unsubstituted alkoxyalkyl
25 groups, substituted or unsubstituted aryloxyalkyl groups, substituted or
unsubstituted hydroxyalkyl groups, or substituted or unsubstituted
heterocyclyloxyalkyl groups;

WO 02/18383

PCT/US01/41942

-10-

R^{15} is selected from H, substituted or unsubstituted alkyl groups, substituted or unsubstituted aryl groups, or substituted or unsubstituted heterocyclyl groups;

R^{16} is selected from H, substituted or unsubstituted alkyl groups, substituted or unsubstituted aryl groups, substituted or unsubstituted heterocyclyl groups, $-C(=O)H$, $-C(=O)$ -alkyl groups, $-C(=O)$ -aryl groups, $-C(=O)NH_2$, $-C(=O)NH$ (alkyl) groups, $-C(=O)NH$ (aryl) groups, $-C(=O)N$ (alkyl)₂ groups, $-C(=O)N$ (aryl)₂ groups, $-C(=O)N$ (alkyl)(aryl) groups, $-C(=O)O$ -alkyl groups, $-C(=O)O$ -aryl groups, substituted or unsubstituted aminoalkyl groups, substituted or unsubstituted alkylaminoalkyl groups, substituted or unsubstituted dialkylaminoalkyl groups, substituted or unsubstituted arylaminoalkyl groups, substituted or unsubstituted diarylaminoalkyl groups, substituted or unsubstituted (alkyl)(aryl)aminoalkyl groups, substituted or unsubstituted heterocyclylalkyl groups, $-C(=O)$ -heterocyclyl groups, $-C(=O)$ -O-heterocyclyl groups, $-C(=O)NH$ (heterocyclyl) groups, $-C(=O)$ -N(heterocyclyl)₂ groups, $-C(=O)$ -N(alkyl)(heterocyclyl) groups, $-C(=O)$ -N(aryl)(heterocyclyl) groups, substituted or unsubstituted heterocyclylaminoalkyl groups, substituted and unsubstituted diheterocyclylaminoalkyl groups, substituted and unsubstituted (heterocyclyl)(alkyl)aminoalkyl groups, substituted and unsubstituted (heterocyclyl)(aryl)aminoalkyl groups, substituted or unsubstituted hydroxyalkyl groups, substituted or unsubstituted alkoxyalkyl groups, substituted or unsubstituted aryloxyalkyl groups, or substituted or unsubstituted heterocycloxyalkyl groups; and

R^{17} , R^{19} , and R^{20} may be the same or different and are independently selected from H, $-NH_2$, $-NH$ (alkyl) groups, $-NH$ (aryl) groups, $-N$ (alkyl)₂ groups, $-N$ (aryl)₂ groups, $-N$ (alkyl)(aryl) groups, $-NH$ (heterocyclyl) groups, $-N$ (heterocyclyl)(alkyl) groups, $-N$ (heterocyclyl)(aryl) groups, $-N$ (heterocyclyl)₂ groups, substituted and unsubstituted alkyl groups, substituted and unsubstituted aryl groups, $-OH$, substituted and unsubstituted alkoxy groups, substituted and

WO 02/18383

PCT/US01/41942

-11-

unsubstituted heterocyclyl groups, substituted and unsubstituted aryloxy groups, heterocyclyloxy groups, -NHOH, -N(alkyl)OH groups, -N(aryl)OH groups, -N(alkyl)O-alkyl groups, -N(aryl)O-alkyl groups, -N(alkyl)O-aryl groups, and -N(aryl)O-aryl groups.

- 5 Preferred compounds having the structure I are provided where Y is selected from -OH, -OR⁸ groups, or -NR¹⁰R¹¹ groups, or more preferably is a -NR¹⁰R¹¹ group.

- Still other preferred compounds having the structure I are provided in which Z is an NR¹³ group and the rest of the compound is consistent with any of the
10 above-described compounds.

In still other preferred compounds of structure I, R⁴ and R⁷ are hydrogen, R⁶ and R⁷ are selected from hydrogen or an alkyl group having from 1 to 4 carbon atoms, and the rest of the compound is consistent with any of the above-described compounds.

- 15 Still other compounds having the formula of structure I are provided in which R⁵ or R⁶ is an -OR¹⁴ group and R¹⁴ is an alkyl, aryl, heterocyclyl, or heterocyclylalkyl group and the rest of the molecule is consistent with any of the above-described compounds.

- In still further preferred compounds having the formula of structure
20 I, R⁵ or R⁶ is a -OCH₂(CH₂)_q(heterocyclyl) group where q is 0, 1, 2, 3, or 4 and the rest of the compound is consistent with any of the above-described compounds.

- Other preferred compounds having the structure I are provided in which R¹⁷ is selected from substituted or unsubstituted alkyl groups, substituted or unsubstituted aryl groups, -NH₂, -NH(alkyl) groups, -N(alkyl)₂ groups, -NH(aryl)
25 groups, -N(aryl)₂ groups, -N(alkyl)(aryl) groups, -NH(heterocyclyl) groups, -N(heterocyclyl)(alkyl) groups, -N(heterocyclyl)(aryl) groups, -N(heterocyclyl)₂ groups, or N-containing heterocycles, and the N-containing heterocycles are bonded

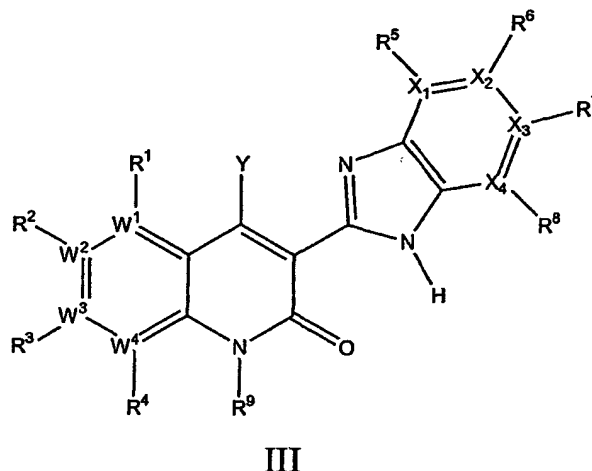
WO 02/18383

PCT/US01/41942

-12-

to the carbonyl carbon of the $-C(=O)-R^{17}$ group through either a nitrogen atom or a carbon atom in the rings of the N-containing heterocycles.

The present invention also provides compounds having the structure III. The invention also provides tautomers of the compounds, pharmaceutically acceptable salts of the compounds, and pharmaceutically acceptable salts of the tautomers. Structure III has the following formula:



where:

10 $W^1, W^2, W^3,$ and W^4 are selected from C or N, and at least one of $W^1, W^2, W^3,$ or W^4 is N;

$X^1, X^2, X^3,$ and X^4 are selected from C or N, and at least one of $X^1, X^2, X^3,$ or X^4 is N;

15 Y is selected from H, $-OH,$ $-OR^{10}$ groups, $-SH,$ $-SR^{11}$ groups, $-NR^{12}R^{13}$ groups, $-CN,$ $-C(=O)-R^{14}$ groups, substituted or unsubstituted alkyl groups, substituted or unsubstituted alkenyl groups, substituted or unsubstituted alkynyl groups, substituted or unsubstituted aralkyl groups, substituted or unsubstituted heterocyclalkyl groups, substituted or unsubstituted alkylaminoalkyl groups, substituted or unsubstituted dialkylaminoalkyl groups, substituted or

WO 02/18383

PCT/US01/41942

-13-

unsubstituted arylaminoalkyl groups, substituted or unsubstituted diarylaminoalkyl groups, substituted or unsubstituted (alkyl)(aryl)aminoalkyl groups, substituted or unsubstituted heterocyclylaminoalkyl groups, substituted and unsubstituted diheterocyclylaminoalkyl groups, substituted and unsubstituted

5 (heterocyclyl)(alkyl)aminoalkyl groups, substituted and unsubstituted (heterocyclyl)(aryl)aminoalkyl groups, substituted or unsubstituted heterocyclyl groups, substituted or unsubstituted aryl groups, substituted or unsubstituted hydroxyalkyl groups, substituted or unsubstituted alkoxyalkyl groups, substituted or unsubstituted aryloxyalkyl groups, or substituted or unsubstituted

10 heterocyclyloxyalkyl groups;

R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , and R^8 may be the same or different and are independently selected from H, Cl, Br, F, I, $-NO_2$, $-CN$, $-OH$, $-OR^{15}$ groups, $-NR^{16}R^{17}$ groups, $-C(=O)R^{18}$ groups, $-SH$, $-SR^{19}$ groups, $-S(=O)R^{20}$ groups, $S(=O)_2R^{19}$ groups, substituted or unsubstituted amidinyl groups, substituted or

15 unsubstituted guanidinyl groups, substituted or unsubstituted primary, secondary, or tertiary alkyl groups, substituted or unsubstituted aryl groups, substituted or unsubstituted alkenyl groups, substituted or unsubstituted alkynyl groups, substituted or unsubstituted heterocyclyl groups, substituted or unsubstituted alkylaminoalkyl groups, substituted or unsubstituted dialkylaminoalkyl groups,

20 substituted or unsubstituted arylaminoalkyl groups, substituted or unsubstituted diarylaminoalkyl groups, substituted or unsubstituted (alkyl)(aryl)aminoalkyl groups, substituted or unsubstituted heterocyclylalkyl groups, substituted or unsubstituted aminoalkyl groups, substituted or unsubstituted heterocyclylaminoalkyl groups, substituted and unsubstituted

25 diheterocyclylaminoalkyl groups, substituted and unsubstituted (alkyl)(heterocyclyl)aminoalkyl groups, substituted and unsubstituted (aryl)(heterocyclyl)aminoalkyl groups, substituted or unsubstituted hydroxyalkyl groups, substituted or unsubstituted alkoxyalkyl groups, substituted or unsubstituted aryloxyalkyl groups, or substituted or unsubstituted heterocyclyloxyalkyl groups,

30 and R^1 is absent or H if W^1 is N, R^2 is absent or H if W^2 is N, R^3 is absent or H if

WO 02/18383

PCT/US01/41942

-14-

W³ is N, R⁴ is absent or H if W⁴ is N, R⁵ is absent or H if X¹ is N, R⁶ is absent or H if X² is N, R⁷ is absent or H if X³ is N, and R⁸ is absent or H if X⁴ is N;

R⁹ is selected from H, -OH, substituted or unsubstituted alkoxy groups, substituted or unsubstituted aryloxy groups, -NH₂, substituted or
5 unsubstituted alkylamino groups, substituted or unsubstituted arylamino groups, substituted or unsubstituted dialkylamino groups, substituted or unsubstituted diarylamino groups, substituted or unsubstituted (alkyl)(aryl)amino groups, substituted or unsubstituted alkyl groups, substituted or unsubstituted aryl groups, -C(=O)H, -C(=O)-alkyl groups, or -C(=O)-aryl groups;

10 R¹⁰ is selected from substituted or unsubstituted alkyl groups, substituted or unsubstituted aryl groups, substituted or unsubstituted heterocyclyl groups, substituted or unsubstituted heterocyclylalkyl groups, -C(=O)H, -C(=O)-alkyl groups, -C(=O)-aryl groups, -C(=O)O-alkyl groups, -C(=O)O-aryl groups, -C(=O)NH₂, -C(=O)NH(alkyl) groups, -C(=O)NH(aryl) groups,
15 -C(=O)N(alkyl)₂ groups, -C(=O)N(aryl)₂ groups, -C(=O)N(alkyl)(aryl) groups, -NH₂, -NH(alkyl) groups, -NH(aryl) groups, -N(alkyl)₂ groups, -N(alkyl)(aryl) groups, -N(aryl)₂ groups, -C(=O)NH(heterocyclyl) groups, -C(=O)N(heterocyclyl)₂ groups, -C(=O)N(alkyl)(heterocyclyl) groups, or -C(=O)N(aryl)(heterocyclyl) groups;

20 R¹⁰ and R¹⁹ may be the same or different and are independently selected from substituted or unsubstituted alkyl groups, or substituted or unsubstituted aryl groups;

R¹² is selected from H, substituted or unsubstituted alkyl groups, substituted or unsubstituted aryl groups, or substituted or unsubstituted heterocyclyl
25 groups;

R¹³ is selected from H, substituted or unsubstituted alkyl groups, substituted or unsubstituted aryl groups, substituted or unsubstituted heterocyclyl groups, -OH, alkoxy groups, aryloxy groups, -NH₂, substituted or unsubstituted

WO 02/18383

PCT/US01/41942

-15-

heterocyclylalkyl groups, substituted or unsubstituted aminoalkyl groups, substituted or unsubstituted alkylaminoalkyl groups, substituted or unsubstituted dialkylaminoalkyl groups, substituted or unsubstituted arylaminoalkyl groups, substituted or unsubstituted diarylaminoalkyl groups, substituted or unsubstituted (alkyl)(aryl)aminoalkyl groups, substituted or unsubstituted alkylamino groups, substituted or unsubstituted arylamino groups, substituted or unsubstituted dialkylamino groups, substituted or unsubstituted diarylamino groups, substituted or unsubstituted (alkyl)(aryl)amino groups, -C(=O)H, -C(=O)-alkyl groups, -C(=O)-aryl groups, -C(=O)O-alkyl groups, -C(=O)O-aryl groups, -C(=O)NH₂, -C(=O)NH(alkyl) groups, -C(=O)NH(aryl) groups, -C(=O)N(alkyl)₂ groups, -C(=O)N(aryl)₂ groups, -C(=O)N(alkyl)(aryl) groups, -C(=O)-heterocyclyl groups, -C(=O)-O-heterocyclyl groups, -C(=O)NH(heterocyclyl) groups, -C(=O)-N(heterocyclyl)₂ groups, -C(=O)-N(alkyl)(heterocyclyl) groups, -C(=O)-N(aryl)(heterocyclyl) groups, substituted or unsubstituted heterocyclylaminoalkyl groups, substituted or unsubstituted hydroxyalkyl groups, substituted or unsubstituted alkoxyalkyl groups, substituted or unsubstituted aryloxyalkyl groups, or substituted or unsubstituted heterocyclyloxyalkyl groups;

R¹⁴ is selected from H, -OH, alkoxy groups, aryloxy groups, -NH₂, -NH(alkyl) groups, -NH(aryl) groups, -N(alkyl)₂ groups, -N(aryl)₂ groups, -N(alkyl)(aryl) groups, substituted or unsubstituted alkyl groups, substituted or unsubstituted aryl groups, -NH(heterocyclyl) groups, -N(heterocyclyl)₂ groups, -N(alkyl)(heterocyclyl) groups, or -N(aryl)(heterocyclyl) groups;

R¹⁵ is selected from substituted or unsubstituted alkyl groups, substituted or unsubstituted aryl groups, substituted or unsubstituted heterocyclyl groups, substituted or unsubstituted heterocyclylalkyl groups, -C(=O)H, -C(=O)-alkyl groups, -C(=O)-aryl groups, -C(=O)-heterocyclyl groups, -C(=O)NH₂, -C(=O)NH(alkyl) groups, -C(=O)NH(aryl) groups, -C(=O)N(alkyl)₂ groups, -C(=O)N(aryl)₂ groups, -C(=O)N(alkyl)(aryl) groups, -C(=O)NH-heterocyclyl groups, -C(=O)N-(heterocyclyl)₂ groups,

WO 02/18383

PCT/US01/41942

-16-

-C(=O)N(alkyl)(heterocyclyl) groups, -C(=O)N(aryl)(heterocyclyl) groups, substituted or unsubstituted aminoalkyl groups, substituted or unsubstituted alkylaminoalkyl groups, substituted or unsubstituted dialkylaminoalkyl groups, substituted or unsubstituted arylaminoalkyl groups, substituted or unsubstituted diarylaminoalkyl groups, substituted or unsubstituted (alkyl)(aryl)aminoalkyl groups, substituted or unsubstituted heterocyclylaminoalkyl groups, substituted or unsubstituted diheterocyclylaminoalkyl groups, substituted or unsubstituted (heterocyclyl)(alkyl)aminoalkyl groups, substituted or unsubstituted (heterocyclyl)(aryl)aminoalkyl groups, substituted or unsubstituted alkoxyalkyl groups, substituted or unsubstituted aryloxyalkyl groups, substituted or unsubstituted hydroxyalkyl groups, or substituted or unsubstituted heterocycliloxyalkyl groups;

R¹⁶ is selected from H, substituted or unsubstituted alkyl groups, substituted or unsubstituted aryl groups, or substituted or unsubstituted heterocyclyl groups;

R¹⁷ is selected from H, substituted or unsubstituted alkyl groups, substituted or unsubstituted aryl groups, substituted or unsubstituted heterocyclyl groups, -C(=O)H, -C(=O)-alkyl groups, -C(=O)-aryl groups, -C(=O)NH₂, -C(=O)NH(alkyl) groups, -C(=O)NH(aryl) groups, -C(=O)N(alkyl)₂ groups, -C(=O)N(aryl)₂ groups, -C(=O)N(alkyl)(aryl) groups, -C(=O)O-alkyl groups, -C(=O)O-aryl groups, substituted or unsubstituted aminoalkyl groups, substituted or unsubstituted alkylaminoalkyl groups, substituted or unsubstituted dialkylaminoalkyl groups, substituted or unsubstituted arylaminoalkyl groups, substituted or unsubstituted diarylaminoalkyl groups, substituted or unsubstituted (aryl)(alkyl)aminoalkyl groups, substituted or unsubstituted heterocyclylalkyl groups, -C(=O)-heterocyclyl groups, -C(=O)-O-heterocyclyl groups, -C(=O)NH(heterocyclyl) groups, -C(=O)-N(heterocyclyl)₂ groups, -C(=O)-N(alkyl)(heterocyclyl) groups, -C(=O)-N(aryl)(heterocyclyl) groups, substituted or unsubstituted heterocyclylaminoalkyl groups, substituted and

WO 02/18383

PCT/US01/41942

-17-

unsubstituted diheterocyclylaminoalkyl groups, substituted and unsubstituted (heterocyclyl)(alkyl)aminoalkyl groups, substituted and unsubstituted (heterocyclyl)(aryl)aminoalkyl groups, substituted or unsubstituted hydroxyalkyl groups, substituted or unsubstituted alkoxyalkyl groups, substituted or unsubstituted
5 aryloxyalkyl groups, or substituted or unsubstituted heterocyclyloxyalkyl groups; and

R^{18} , R^{20} , and R^{21} may be the same or different and are independently selected from H, $-NH_2$, $-NH(alkyl)$ groups, $-NH(aryl)$ groups, $-N(alkyl)_2$ groups, $-N(aryl)_2$ groups, $-N(alkyl)(aryl)$ groups, $-NH(heterocyclyl)$ groups,
10 $-N(heterocyclyl)(alkyl)$ groups, $-N(heterocyclyl)(aryl)$ groups, $-N(heterocyclyl)_2$ groups, substituted or unsubstituted alkyl groups, substituted or unsubstituted aryl groups, $-OH$, substituted or unsubstituted alkoxy groups, substituted or unsubstituted heterocyclyl groups, substituted or unsubstituted aryloxy groups, heterocyclyloxy groups, $-NHOH$, $-N(alkyl)OH$ groups, $-N(aryl)OH$ groups,
15 $-N(alkyl)O-alkyl$ groups, $-N(aryl)O-alkyl$ groups, $-N(alkyl)O-aryl$ groups, and $-N(aryl)O-aryl$ groups.

Preferred compounds having structure III are also provided where one of W^1 , W^2 , W^3 , or W^4 is N.

Preferred compounds having structure III are also provided where
20 one of X^1 , X^2 , X^3 , or X^4 is N.

Preferred compounds having structure III are also provided where Y is selected from H, $-OH$, $-OR^{10}$ groups, or $-NR^{12}R^{13}$ groups, or more preferably is a $-NR^{12}R^{13}$ group.

Still other preferred compounds having structure III are provided
25 where R^5 is H, X^4 is N, R^6 and R^7 are selected from H or alkyl groups having from one to four carbon atoms, and the rest of the compound is consistent with any of the above-described compounds.

WO 02/18383

PCT/US01/41942

-18-

Still other compounds of structure III are provided in which R⁶ or R⁷ is an -OR¹⁵ group and R¹⁵ is an alkyl, aryl, heterocyclyl, or heterocyclylalkyl group and the rest of the molecule is consistent with any of the above-described compounds.

- 5 In still further preferred compounds of structure III, R⁶ or R⁷ is a -OCH₂(CH₂)_q(heterocyclyl) group, q is 0, 1, 2, 3, or 4, and the rest of the compound is consistent with any of the above-described compounds.

- Other preferred compounds having the structure III are provided in which R¹⁸ is selected from substituted or unsubstituted alkyl groups, substituted or
10 unsubstituted aryl groups, -NH₂, -NH(alkyl) groups, -N(alkyl)₂ groups, -NH(aryl) groups, -N(aryl)₂ groups, -N(alkyl)(aryl) groups, -NH(heterocyclyl) groups, -N(heterocyclyl)(alkyl) groups, -N(heterocyclyl)(aryl) groups, -N(heterocyclyl)₂ groups, or N-containing heterocycles, and the N-containing heterocycles are bonded to the carbonyl carbon of the -C(=O)-R¹⁸ group through either a nitrogen atom or a
15 carbon atom in the rings of the N-containing heterocycles.

Pharmaceutical formulations according to the present invention are provided which include any of the compounds described above in combination with a pharmaceutically acceptable carrier.

- A method of treating a patient in need of an inhibitor of vascular
20 endothelial growth factor receptor tyrosine kinase is provided which includes administering an effective amount of the pharmaceutical formulation according to the present invention to a patient in need thereof.

Further objects, features and advantages of the invention will be apparent from the following detailed description.

WO 02/18383

PCT/US01/41942

-19-

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides novel compounds that act as antagonists of receptor tyrosine kinases, and, more particularly, as inhibitors of bFGF and VEGF-RTK function. The compounds provided herein can be
5 formulated into pharmaceutical formulations that are useful in treating patients with a need for an inhibitor of VEGF-RTK, especially, in particular embodiments, to provide compositions and methods for reducing capillary proliferation and in the treatment of cancer.

The following abbreviations and definitions are used throughout this
10 application:

“VEGF” is an abbreviation that stands for vascular endothelial growth factor.

“RTK” is an abbreviation that stands for receptor tyrosine kinase.

“VEGF-RTK” is an abbreviation that stands for vascular endothelial
15 growth factor receptor tyrosine kinase.

“Flt-1” is an abbreviation that stands for fms-like tyrosine kinase-1, also known as vascular endothelial growth factor receptor-1 or “VEGFR1”.

“KDR” is an abbreviation that stands for kinase-insert domain tyrosine kinase, also known as vascular endothelial growth factor receptor-2 or
20 “VEGFR2”.

“bFGF” is an abbreviation that stands for basic fibroblast growth factor.

“bFGFR” is an abbreviation that stands for basic fibroblast growth factor receptor.

WO 02/18383

PCT/US01/41942

-20-

Generally, reference to a certain element such as hydrogen or H is meant to include all isotopes of that element. For example, if an R group is defined to include hydrogen or H, it also includes deuterium and tritium.

The phrase "unsubstituted alkyl" refers to alkyl groups that do not contain heteroatoms. Thus the phrase includes straight chain alkyl groups such as methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl and the like. The phrase also includes branched chain isomers of straight chain alkyl groups, including but not limited to, the following which are provided by way of example: $-\text{CH}(\text{CH}_3)_2$, $-\text{CH}(\text{CH}_3)(\text{CH}_2\text{CH}_3)$, $-\text{CH}(\text{CH}_2\text{CH}_3)_2$, $-\text{C}(\text{CH}_3)_3$, $-\text{C}(\text{CH}_2\text{CH}_3)_3$, $-\text{CH}_2\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{CH}(\text{CH}_3)(\text{CH}_2\text{CH}_3)$, $-\text{CH}_2\text{CH}(\text{CH}_2\text{CH}_3)_2$, $-\text{CH}_2\text{C}(\text{CH}_3)_3$, $-\text{CH}_2\text{C}(\text{CH}_2\text{CH}_3)_3$, $-\text{CH}(\text{CH}_3)\text{CH}(\text{CH}_3)(\text{CH}_2\text{CH}_3)$, $-\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)(\text{CH}_2\text{CH}_3)$, $-\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_2\text{CH}_3)_2$, $-\text{CH}_2\text{CH}_2\text{C}(\text{CH}_3)_3$, $-\text{CH}_2\text{CH}_2\text{C}(\text{CH}_2\text{CH}_3)_3$, $-\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}(\text{CH}_3)_2$, $-\text{CH}(\text{CH}_3)\text{CH}(\text{CH}_3)\text{CH}(\text{CH}_3)_2$, $-\text{CH}(\text{CH}_2\text{CH}_3)\text{CH}(\text{CH}_3)\text{CH}(\text{CH}_3)(\text{CH}_2\text{CH}_3)$, and others. The phrase also includes cyclic alkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl and such rings substituted with straight and branched chain alkyl groups as defined above. The phrase also includes polycyclic alkyl groups such as, but not limited to, adamantyl and norbornyl and such rings substituted with straight and branched chain alkyl groups as defined above. Thus the phrase unsubstituted alkyl groups includes primary alkyl groups, secondary alkyl groups, and tertiary alkyl groups. Unsubstituted alkyl groups may be bonded to one or more carbon atom(s), oxygen atom(s), nitrogen atom(s), and/or sulfur atom(s) in the parent compound. Preferred unsubstituted alkyl groups include straight and branched chain alkyl groups and cyclic alkyl groups having 1 to 20 carbon atoms. More preferred such unsubstituted alkyl groups have from 1 to 10 carbon atoms while even more preferred such groups have from 1 to 5 carbon atoms. Most preferred unsubstituted alkyl groups include straight and branched chain alkyl groups having from 1 to 3 carbon atoms and include methyl, ethyl, propyl, and $-\text{CH}(\text{CH}_3)_2$.

WO 02/18383

PCT/US01/41942

-21-

The phrase "substituted alkyl" refers to an unsubstituted alkyl group as defined above in which one or more bonds to a carbon(s) or hydrogen(s) are replaced by a bond to non-hydrogen and non-carbon atoms such as, but not limited to, a halogen atom in halides such as F, Cl, Br, and I; and oxygen atom in groups such as hydroxyl groups, alkoxy groups, aryloxy groups, and ester groups; a sulfur atom in groups such as thiol groups, alkyl and aryl sulfide groups, sulfone groups, sulfonyl groups, and sulfoxide groups; a nitrogen atom in groups such as amines, amides, alkylamines, dialkylamines, arylamines, alkylarylamines, diarylamines, N-oxides, imides, and enamines; a silicon atom in groups such as in trialkylsilyl groups, dialkylarylsilyl groups, alkylarylsilyl groups, and triarylsilyl groups; and other heteroatoms in various other groups. Substituted alkyl groups also include groups in which one or more bonds to a carbon(s) or hydrogen(s) atom is replaced by a bond to a heteroatom such as oxygen in carbonyl, carboxyl, and ester groups; nitrogen in groups such as imines, oximes, hydrazones, and nitriles. Substituted alkyl groups include, among others, alkyl groups in which one or more bonds to a carbon or hydrogen atom is/are replaced by one or more bonds to fluorine atoms. One Example of a substituted alkyl group is the trifluoromethyl group and other alkyl groups that contain the trifluoromethyl group. Other alkyl groups include those in which one or more bonds to a carbon or hydrogen atom is replaced by a bond to an oxygen atom such that the substituted alkyl group contains a hydroxyl, alkoxy, aryloxy, or heterocycloxy group. Still other substituted alkyl groups include alkyl groups that have an amine, alkylamine, dialkylamine, arylamine, (alkyl)(aryl)amine, diarylamine, heterocyclamine, (alkyl)(heterocycl)amine, (aryl)(heterocycl)amine, or diheterocyclamine group.

The phrase "unsubstituted aryl" refers to aryl groups that do not contain heteroatoms. Thus the phrase includes, but is not limited to, groups such as phenyl, biphenyl, anthracenyl, naphthenyl by way of example. Although the phrase "unsubstituted aryl" includes groups containing condensed rings such as naphthalene, it does not include aryl groups that have other groups such as alkyl or halo groups bonded to one of the ring members, as aryl groups such as tolyl are

WO 02/18383

PCT/US01/41942

-22-

considered herein to be substituted aryl groups as described below. A preferred unsubstituted aryl group is phenyl. Unsubstituted aryl groups may be bonded to one or more carbon atom(s), oxygen atom(s), nitrogen atom(s), and/or sulfur atom(s) in the parent compound, however.

5 The phrase "substituted aryl group" has the same meaning with respect to unsubstituted aryl groups that substituted alkyl groups had with respect to unsubstituted alkyl groups. However, a substituted aryl group also includes aryl groups in which one of the aromatic carbons is bonded to one of the non-carbon or non-hydrogen atoms described above and also includes aryl groups in which one or
10 more aromatic carbons of the aryl group is bonded to a substituted and/or unsubstituted alkyl group. Thus, the phrase "substituted aryl" includes, but is not limited to tolyl, and hydroxyphenyl among others.

 The phrase "unsubstituted alkenyl" refers to straight and branched chain and cyclic groups such as those described with respect to unsubstituted alkyl
15 groups as defined above, except that at least one double bond exists between two carbon atoms. Examples include, but are not limited to vinyl, $-\text{CH}=\text{C}(\text{H})(\text{CH}_3)$, $-\text{CH}=\text{C}(\text{CH}_3)_2$, $-\text{C}(\text{CH}_3)=\text{C}(\text{H})_2$, $-\text{C}(\text{CH}_3)=\text{C}(\text{H})(\text{CH}_3)$, $-\text{C}(\text{CH}_2\text{CH}_3)=\text{CH}_2$, cyclohexenyl, cyclopentenyl, cyclohexadienyl, butadienyl, pentadienyl, and hexadienyl among others.

20 The phrase "substituted alkenyl" has the same meaning with respect to unsubstituted alkenyl groups that substituted alkyl groups had with respect to unsubstituted alkyl groups. A substituted alkenyl group includes alkenyl groups in which a non-carbon or non-hydrogen atom is bonded to a carbon double bonded to another carbon and those in which one of the non-carbon or non-hydrogen atoms is
25 bonded to a carbon not involved in a double bond to another carbon.

 The phrase "unsubstituted alkynyl" refers to straight and branched chain groups such as those described with respect to unsubstituted alkyl groups as defined above, except that at least one triple bond exists between two carbon atoms.

WO 02/18383

PCT/US01/41942

-23-

Examples include, but are not limited to $-C\equiv C(H)$, $-C\equiv C(CH_3)$, $-C\equiv C(CH_2CH_3)$, $-C(H)_2C\equiv C(H)$, $-C(H)_2C\equiv C(CH_3)$, and $-C(H)_2C\equiv C(CH_2CH_3)$ among others.

The phrase "substituted alkynyl" has the same meaning with respect to unsubstituted alkynyl groups that substituted alkyl groups had with respect to unsubstituted alkyl groups. A substituted alkynyl group includes alkynyl groups in which a non-carbon or non-hydrogen atom is bonded to a carbon triple bonded to another carbon and those in which a non-carbon or non-hydrogen atom is bonded to a carbon not involved in a triple bond to another carbon.

The phrase "unsubstituted aralkyl" refers to unsubstituted alkyl groups as defined above in which a hydrogen or carbon bond of the unsubstituted alkyl group is replaced with a bond to an aryl group as defined above. For example, methyl ($-CH_3$) is an unsubstituted alkyl group. If a hydrogen atom of the methyl group is replaced by a bond to a phenyl group, such as if the carbon of the methyl were bonded to a carbon of benzene, then the compound is an unsubstituted aralkyl group (i.e. a benzyl group). Thus the phrase includes, but is not limited to, groups such as benzyl, diphenylmethyl, and 1-phenylethyl ($-CH(C_6H_5)(CH_3)$) among others.

The phrase "substituted aralkyl" has the same meaning with respect to unsubstituted aralkyl groups that substituted aryl groups had with respect to unsubstituted aryl groups. However, a substituted aralkyl group also includes groups in which a carbon or hydrogen bond of the alkyl part of the group is replaced by a bond to a non-carbon or a non-hydrogen atom. Examples of substituted aralkyl groups include, but are not limited to, $-CH_2C(=O)(C_6H_5)$, and $-CH_2(2\text{-methylphenyl})$ among others.

The phrase "unsubstituted heterocyclyl" refers to both aromatic and nonaromatic ring compounds including monocyclic, bicyclic, and polycyclic ring compounds such as, but not limited to, quinuclidyl, containing 3 or more ring members of which one or more is a heteroatom such as, but not limited to, N, O,

WO 02/18383

PCT/US01/41942

-24-

and S. Although the phrase "unsubstituted heterocyclyl" includes condensed heterocyclic rings such as benzimidazolyl, it does not include heterocyclyl groups that have other groups such as alkyl or halo groups bonded to one of the ring members as compounds such as 2-methylbenzimidazolyl are substituted heterocyclyl groups. Examples of heterocyclyl groups include, but are not limited to:

5 unsaturated 3 to 8 membered rings containing 1 to 4 nitrogen atoms such as, but not limited to pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, dihydropyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl (e.g. 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl etc.), tetrazolyl, (e.g. 1H-tetrazolyl, 2H-tetrazolyl,

10 etc.); saturated 3 to 8 membered rings containing 1 to 4 nitrogen atoms such as, but not limited to, pyrrolidinyl, imidazolidinyl, piperidinyl, piperazinyl; condensed unsaturated heterocyclic groups containing 1 to 4 nitrogen atoms such as, but not limited to, indolyl, isoindolyl, indolinyl, indolizynyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl; unsaturated 3 to 8 membered rings containing

15 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms such as, but not limited to, oxazolyl, isoxazolyl, oxadiazolyl (e.g. 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.); saturated 3 to 8 membered rings containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms such as, but not limited to, morpholinyl; unsaturated condensed heterocyclic groups containing 1 to 2 oxygen atoms and 1 to 3 nitrogen

20 atoms, for example, benzoxazolyl, benzoxadiazolyl, benzoxazinyl (e.g. 2H-1,4-benzoxazinyl etc.); unsaturated 3 to 8 membered rings containing 1 to 3 sulfur atoms and 1 to 3 nitrogen atoms such as, but not limited to, thiazolyl, isothiazolyl, thiadiazolyl (e.g. 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.); saturated 3 to 8 membered rings containing 1 to 2 sulfur atoms

25 and 1 to 3 nitrogen atoms such as, but not limited to, thiazolodiny; saturated and unsaturated 3 to 8 membered rings containing 1 to 2 sulfur atoms such as, but not limited to, thienyl, dihydrodithiynyl, dihydrodithionyl, tetrahydrothiophene, tetrahydrothiopyran; unsaturated condensed heterocyclic rings containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms such as, but not limited to, benzothiazolyl,

30 benzothiadiazolyl, benzothiazinyl (e.g. 2H-1,4-benzothiazinyl, etc.),

WO 02/18383

PCT/US01/41942

-25-

dihydrobenzothiazinyl (e.g. 2H-3,4-dihydrobenzothiazinyl, etc.), unsaturated 3 to 8 membered rings containing oxygen atoms such as, but not limited to furyl; unsaturated condensed heterocyclic rings containing 1 to 2 oxygen atoms such as benzodioxolyl (e.g. 1,3-benzodioxolyl, etc.); unsaturated 3 to 8 membered rings
5 containing an oxygen atom and 1 to 2 sulfur atoms such as, but not limited to, dihydrooxathiinyl; saturated 3 to 8 membered rings containing 1 to 2 oxygen atoms and 1 to 2 sulfur atoms such as 1,4-oxathiane; unsaturated condensed rings containing 1 to 2 sulfur atoms such as benzothienyl, benzodithiinyl; and unsaturated condensed heterocyclic rings containing an oxygen atom and 1 to 2 oxygen atoms
10 such as benzoxathiinyl. Heterocyclyl group also include those described above in which one or more S atoms in the ring is double bonded to one or two oxygen atoms (sulfoxides and sulfones). For example, heterocyclyl groups include tetrahydrothiophene, tetrahydrothiophene oxide, and tetrahydrothiophene 1,1-dioxide. Preferred heterocyclyl groups contain 5 or 6 ring members. More
15 preferred heterocyclyl groups include morpholine, piperazine, piperidine, pyrrolidine, imidazole, pyrazole, 1,2,3-triazole, 1,2,4-triazole, tetrazole, thiomorpholine, pyrrole, homopiperazine, oxazolidin-2-one, pyrrolidin-2-one, oxazole, thiazole, isoxazole, furan, and tetrahydrofuran.

The phrase "substituted heterocyclyl" refers to an unsubstituted
20 heterocyclyl group as defined above in which one of the ring members is bonded to a non-hydrogen atom such as described above with respect to substituted alkyl groups and substituted aryl groups. Examples, include, but are not limited to, 2-methylbenzimidazolyl, 5-methylbenzimidazolyl, 5-chlorobenzthiazolyl, 1-methyl piperazinyl, and 2-chloropyridyl among others.

25 The phrase "unsubstituted heterocyclylalkyl" refers to unsubstituted alkyl groups as defined above in which a hydrogen or carbon bond of the unsubstituted alkyl group is replaced with a bond to a heterocyclyl group as defined above. For example, methyl (-CH₃) is an unsubstituted alkyl group. If a hydrogen atom of the methyl group is replaced by a bond to a heterocyclyl group, such as if

WO 02/18383

PCT/US01/41942

-26-

the carbon of the methyl were bonded to carbon 2 of pyridine (one of the carbons bonded to the N of the pyridine) or carbons 3 or 4 of the pyridine, then the compound is an unsubstituted heterocyclalkyl group.

The phrase "substituted heterocyclalkyl" has the same meaning
5 with respect to unsubstituted heterocyclalkyl groups that substituted aralkyl groups had with respect to unsubstituted aralkyl groups. However, a substituted heterocyclalkyl group also includes groups in which a non-hydrogen atom is bonded to a heteroatom in the heterocycl group of the heterocyclalkyl group such as, but not limited to, a nitrogen atom in the piperidine ring of a
10 piperidinylalkyl group.

The phrase "unsubstituted alkylaminoalkyl" refers to an unsubstituted alkyl group as defined above in which a carbon or hydrogen bond is replaced by a bond to a nitrogen atom that is bonded to a hydrogen atom and an unsubstituted alkyl group as defined above. For example, methyl ($-\text{CH}_3$) is an unsubstituted alkyl
15 group. If a hydrogen atom of the methyl group is replaced by a bond to a nitrogen atom that is bonded to a hydrogen atom and an ethyl group, then the resulting compound is $-\text{CH}_2-\text{N}(\text{H})(\text{CH}_2\text{CH}_3)$ which is an unsubstituted alkylaminoalkyl group.

The phrase "substituted alkylaminoalkyl" refers to an unsubstituted
20 alkylaminoalkyl group as defined above except where one or more bonds to a carbon or hydrogen atom in one or both of the alkyl groups is replaced by a bond to a non-carbon or non-hydrogen atom as described above with respect to substituted alkyl groups except that the bond to the nitrogen atom in all alkylaminoalkyl groups does not by itself qualify all alkylaminoalkyl groups as being substituted. However,
25 substituted alkylaminoalkyl groups does include groups in which the hydrogen bonded to the nitrogen atom of the group is replaced with a non-carbon and non-hydrogen atom.

WO 02/18383

PCT/US01/41942

-27-

The phrase "unsubstituted dialkylaminoalkyl" refers to an unsubstituted alkyl group as defined above in which a carbon bond or hydrogen bond is replaced by a bond to a nitrogen atom which is bonded to two other similar or different unsubstituted alkyl groups as defined above.

- 5 The phrase "substituted dialkylaminoalkyl" refers to an unsubstituted dialkylaminoalkyl group as defined above in which one or more bonds to a carbon or hydrogen atom in one or more of the alkyl groups is replaced by a bond to a non-carbon and non-hydrogen atom as described with respect to substituted alkyl groups. The bond to the nitrogen atom in all dialkylaminoalkyl groups does not by
10 itself qualify all dialkylaminoalkyl groups as being substituted.

The phrase "unsubstituted heterocycloxyalkyl" refers to an unsubstituted alkyl group as defined above in which a carbon bond or hydrogen bond is replaced by a bond to an oxygen atom which is bonded to an unsubstituted heterocyclyl group as defined above.

- 15 The phrase "substituted heterocycloxyalkyl" refers to an unsubstituted heterocycloxyalkyl group as defined above in which a bond to a carbon or hydrogen group of the alkyl group of the heterocycloxyalkyl group is bonded to a non-carbon and non-hydrogen atom as described above with respect to substituted alkyl groups or in which the heterocyclyl group of the
20 heterocycloxyalkyl group is a substituted heterocyclyl group as defined above.

The phrase "unsubstituted arylaminoalkyl" refers to an unsubstituted alkyl group as defined above in which a carbon bond or hydrogen bond is replaced by a bond to a nitrogen atom which is bonded to at least one unsubstituted aryl group as defined above.

- 25 The phrase "substituted arylaminoalkyl" refers to an unsubstituted arylaminoalkyl group as defined above except where either the alkyl group of the arylaminoalkyl group is a substituted alkyl group as defined above or the aryl group of the arylaminoalkyl group is a substituted aryl group except that the bonds to the

WO 02/18383

PCT/US01/41942

-28-

nitrogen atom in all arylaminoalkyl groups does not by itself qualify all arylaminoalkyl groups as being substituted. However, substituted arylaminoalkyl groups does include groups in which the hydrogen bonded to the nitrogen atom of the group is replaced with a non-carbon and non-hydrogen atom.

5 The phrase "unsubstituted heterocyclaminoalkyl" refers to an unsubstituted alkyl group as defined above in which a carbon or hydrogen bond is replaced by a bond to a nitrogen atom which is bonded to at least one unsubstituted heterocycl group as defined above.

 The phrase "substituted heterocyclaminoalkyl" refers to
10 unsubstituted heterocyclaminoalkyl groups as defined above in which the heterocycl group is a substituted heterocycl group as defined above and/or the alkyl group is a substituted alkyl group as defined above. The bonds to the nitrogen atom in all heterocyclaminoalkyl groups does not by itself qualify all heterocyclaminoalkyl groups as being substituted. However, substituted
15 heterocyclaminoalkyl groups do include groups in which the hydrogen bonded to the nitrogen atom of the group is replaced with a non-carbon and non-hydrogen atom.

 The phrase "unsubstituted alkylaminoalkoxy" refers to an unsubstituted alkyl group as defined above in which a carbon or hydrogen bond is
20 replaced by a bond to an oxygen atom which is bonded to the parent compound and in which another carbon or hydrogen bond of the unsubstituted alkyl group is bonded to a nitrogen atom which is bonded to a hydrogen atom and an unsubstituted alkyl group as defined above.

 The phrase "substituted alkylaminoalkoxy" refers to unsubstituted
25 alkylaminoalkoxy groups as defined above in which a bond to a carbon or hydrogen atom of the alkyl group bonded to the oxygen atom which is bonded to the parent compound is replaced by one or more bonds to a non-carbon and non-hydrogen atoms as discussed above with respect to substituted alkyl groups and/or if the

WO 02/18383

PCT/US01/41942

-29-

hydrogen bonded to the amino group is bonded to a non-carbon and non-hydrogen atom and/or if the alkyl group bonded to the nitrogen of the amine is bonded to a non-carbon and non-hydrogen atom as described above with respect to substituted alkyl groups. The presence of the amine and alkoxy functionality in all

5 alkylaminoalkoxy groups does not by itself qualify all such groups as substituted alkylaminoalkoxy groups.

The phrase "unsubstituted dialkylaminoalkoxy" refers to an unsubstituted alkyl group as defined above in which a carbon or hydrogen bond is replaced by a bond to an oxygen atom which is bonded to the parent compound and

10 in which another carbon or hydrogen bond of the unsubstituted alkyl group is bonded to a nitrogen atom which is bonded to two other similar or different unsubstituted alkyl groups as defined above.

The phrase "substituted dialkylaminoalkoxy" refers to an unsubstituted dialkylaminoalkoxy group as defined above in which a bond to a

15 carbon or hydrogen atom of the alkyl group bonded to the oxygen atom which is bonded to the parent compound is replaced by one or more bonds to a non-carbon and non-hydrogen atoms as discussed above with respect to substituted alkyl groups and/or if one or more of the alkyl groups bonded to the nitrogen of the amine is bonded to a non-carbon and non-hydrogen atom as described above with respect to

20 substituted alkyl groups. The presence of the amine and alkoxy functionality in all dialkylaminoalkoxy groups does not by itself qualify all such groups as substituted dialkylaminoalkoxy groups.

The phrase "unsubstituted heterocyclyloxy" refers to a hydroxyl group (-OH) in which the bond to the hydrogen atom is replaced by a bond to a ring

25 atom of an otherwise unsubstituted heterocyclyl group as defined above.

The phrase "substituted heterocyclyloxy" refers to a hydroxyl group (-OH) in which the bond to the hydrogen atom is replaced by a bond to a ring atom of an otherwise substituted heterocyclyl group as defined above.

WO 02/18383

PCT/US01/41942

-30-

The term "protected" with respect to hydroxyl groups, amine groups, and sulfhydryl groups refers to forms of these functionalities which are protected from undesirable reaction with a protecting group known to those skilled in the art such as those set forth in Protective Groups in Organic Synthesis, Greene, T.W.;

5 Wuts, P. G. M., John Wiley & Sons, New York, NY, (3rd Edition, 1999) which can be added or removed using the procedures set forth therein. Examples of protected hydroxyl groups include, but are not limited to, silyl ethers such as those obtained by reaction of a hydroxyl group with a reagent such as, but not limited to, t-butyldimethyl-chlorosilane, trimethylchlorosilane, triisopropylchlorosilane,

10 triethylchlorosilane; substituted methyl and ethyl ethers such as, but not limited to methoxymethyl ether, methythiomethyl ether, benzyloxymethyl ether, t-butoxymethyl ether, 2-methoxyethoxymethyl ether, tetrahydropyranyl ethers, 1-ethoxyethyl ether, allyl ether, benzyl ether; esters such as, but not limited to, benzoylformate, formate, acetate, trichloroacetate, and trifluoroacetate. Examples of

15 protected amine groups include, but are not limited to, amides such as, formamide, acetamide, trifluoroacetamide, and benzamide; imides, such as phthalimide, and dithiosuccinimide; and others. Examples of protected sulfhydryl groups include, but are not limited to, thioethers such as S-benzyl thioether, and S-4-picolyl thioether; substituted S-methyl derivatives such as hemithio, dithio and aminothio

20 acetals; and others.

A "pharmaceutically acceptable salt" includes a salt with an inorganic base, organic base, inorganic acid, organic acid, or basic or acidic amino acid. As salts of inorganic bases, the invention includes, for example, alkali metals such as sodium or potassium; alkaline earth metals such as calcium and magnesium

25 or aluminum; and ammonia. As salts of organic bases, the invention includes, for example, trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, and triethanolamine. As salts of inorganic acids, the instant invention includes, for example, hydrochloric acid, hydroboric acid, nitric acid, sulfuric acid, and phosphoric acid. As salts of organic acids, the instant invention

30 includes, for example, formic acid, acetic acid, trifluoroacetic acid, fumaric acid,

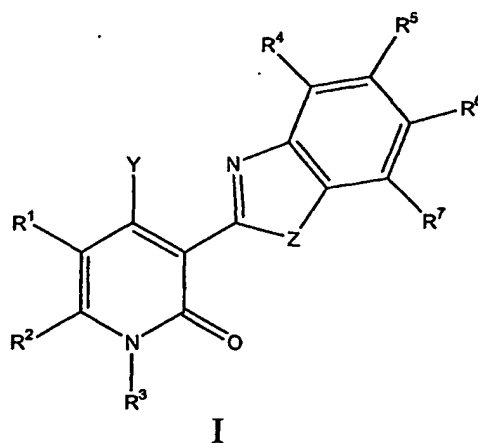
WO 02/18383

PCT/US01/41942

-31-

oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, and p-toluenesulfonic acid. As salts of basic amino acids, the instant invention includes, for example, arginine, lysine and ornithine. Acidic amino acids include, for example, aspartic acid and glutamic acid.

Compounds having the structure I, tautomers of the compounds, pharmaceutically acceptable salts of the compounds, and pharmaceutically acceptable salts of the tautomers have been found to inhibit VEGF-RTK. Structure I has the following formula.



10

In compounds of structure I, Y is selected from -OH, -OR⁸ groups, -SH, -SR⁹ groups, -NR¹⁰R¹¹ groups, -CN, -C(=O)-R¹² groups, substituted or unsubstituted alkyl groups, substituted or unsubstituted alkenyl groups, substituted or unsubstituted alkynyl groups, substituted or unsubstituted aralkyl groups, substituted or unsubstituted heterocyclalkyl groups, substituted or unsubstituted alkylaminoalkyl groups, substituted or unsubstituted dialkylaminoalkyl groups, substituted or unsubstituted arylaminoalkyl groups, substituted or unsubstituted diarylaminoalkyl groups, substituted or unsubstituted (alkyl)(aryl)aminoalkyl groups, substituted or unsubstituted heterocyclaminoalkyl groups, substituted and unsubstituted diheterocyclaminoalkyl groups, substituted and unsubstituted (alkyl)(heterocycl)aminoalkyl groups, substituted and unsubstituted

20

WO 02/18383

PCT/US01/41942

-32-

- (aryl)(heterocyclyl)aminoalkyl groups, substituted or unsubstituted heterocyclyl groups, substituted or unsubstituted aryl groups, substituted or unsubstituted hydroxyalkyl groups, substituted or unsubstituted alkoxyalkyl groups, substituted or unsubstituted aryloxyalkyl groups, or substituted or unsubstituted
- 5 heterocyclyloxyalkyl groups. In more preferred compounds having the structure I, Y is -OH, an -OR⁸ group, or a -NR¹⁰R¹¹ group. More preferably, Y is a -NR¹⁰R¹¹ group, where, one of R¹⁰ or R¹¹ is H or where R¹⁰ and R¹¹ are both H.

- In yet other compounds having the structure I, Y is selected from
- N(CH₃)₂, -NH(CH₃), -NH(CH₂CH₃), -N(CH₂CH₃)₂, -NH(aryl) groups, -N(aryl)₂
- 10 groups, -NHNH₂, -NHN(CH₃)₂, -N(CH₃)NH(CH₃), -NH(CH₂)_mNH₂ groups, -NH(CH₂)_mNH(alkyl) groups, -NH(CH₂)_mN(alkyl)₂ groups, -N(alkyl)(CH₂)_mNH₂ groups, -N(alkyl)(CH₂)_mNH(alkyl) groups, -N(alkyl)(CH₂)_mN(alkyl)₂ groups, -NH(CH₂)_n(heterocyclyl) groups, -N(alkyl)[(CH₂)_n(heterocyclyl)] groups, -NH(CH₂)_mOH groups, -NH(CH₂)_mOCH₃ groups, -NHCH₂CH(NH₂)CH(CH₃)₂,
- 15 -NH(2-aminocyclohexyl), -NH(cyclohexyl), -NHOCH₃, -NH(N-morpholinyl), -NH(quinuclidyl), especially -NH(quinuclid-3-yl), and groups where R¹⁰ and R¹¹ join to form a substituted or unsubstituted saturated 5 or 6 membered N-containing ring, where m is 2, 3, or 4 and n is 0, 1, 2, or 3. Still more preferred compounds of this type are compounds in which Y is -NH(5-benzimidazolyl),
- 20 -NH(CH₂)₂N(CH₃)₂, -NH(CH₂)₂OH, -NH(CH₂)(4-imidazolyl), -NH(CH₂)(3-imidazolyl), -NH(CH₂)(4-pyridyl), -NH(CH₂)(2-pyridyl), -NH(CH₂)(3-pyridyl), -NH(CH₂)(2-tetrahydrofuranyl), -NH(CH₂)(4-piperidinyl), -NH(CH₂)(3-piperidinyl), -NH(CH₂)₂[2-(N-methyl-pyrrolidinyl)], -NH(CH₂)₂(2-pyrrolidinyl), -NH(CH₂)[2-(N-methylpyrrolidinyl)], -NH(CH₂)(2-pyrrolidinyl), -NH(3-
- 25 piperidinyl), or -NH(3-pyrrolidinyl).

Z is O, S, or a NR¹³ group in compounds of structure I. Preferably, Z is a NR¹³ group and, even more preferably, R¹³ is H.

In compounds of structure I, R¹ and R² join to form a 5 to 7 membered substituted or unsubstituted ring including at least one O, N, or S atom.

WO 02/18383

PCT/US01/41942

-33-

In some embodiments, R¹ and R² join together to form a 5 or 6 membered substituted or unsubstituted ring including one N atom, one O atom, or one S atom. In other embodiments R¹ and R² join together to form a 5 or 6 membered ring including two heteroatoms selected from O, N, or S. An example of an

5 embodiment in which R¹ and R² join together to form a 5 membered ring having two N atoms are compounds having the formula IA described below. Another example of an embodiment in which R¹ and R² join together to form a 5 membered ring having two N atoms are compounds having the formula IB described below. An example of an embodiment in which R¹ and R² form a 5 membered ring having

10 one S atom are compounds having the formula IC described below. Examples of embodiments in which R¹ and R² join together to form a 6 membered ring containing one or more N atom are compounds having the formula II below.

R³ and R¹³ may be the same or different in compounds of structure I and may be H, -OH, substituted or unsubstituted alkoxy groups, substituted or

15 unsubstituted aryloxy groups, -NH₂, substituted or unsubstituted alkylamino groups, substituted or unsubstituted arylamino groups, substituted or unsubstituted dialkylamino groups, substituted or unsubstituted diarylamino groups, substituted or unsubstituted (alkyl)(aryl)amino groups, substituted and unsubstituted heterocyclylamino groups, substituted and unsubstituted diheterocyclylamino

20 groups, substituted and unsubstituted (alkyl)(heterocyclyl)amino groups, substituted and unsubstituted (aryl)(heterocyclyl)amino groups, substituted and unsubstituted heterocyclyloxy groups, substituted or unsubstituted alkyl groups, substituted or unsubstituted aryl groups, -C(=O)H, -C(=O)-alkyl groups, or -C(=O)-aryl groups. In more preferred compounds of structure I, R³ is H.

25 R⁴, R⁵, R⁶, and R⁷ may be the same or different in compounds of structure I and are independently selected from H, Cl, Br, F, I, -NO₂, -CN, -OH, -OR¹⁴ groups, -NR¹⁵R¹⁶ groups, -C(=O)R¹⁷ groups, -SH, -SR¹⁸ groups, -S(=O)R¹⁹ groups, S(=O)₂R²⁰ groups, substituted or unsubstituted amidinyl groups, substituted or unsubstituted guanidinyl groups, substituted or unsubstituted primary, secondary,

WO 02/18383

PCT/US01/41942

-34-

- or tertiary alkyl groups, substituted or unsubstituted aryl groups, substituted or unsubstituted alkenyl groups, substituted or unsubstituted alkynyl groups, substituted or unsubstituted heterocyclyl groups, substituted or unsubstituted alkylaminoalkyl groups, substituted or unsubstituted dialkylaminoalkyl groups, substituted or unsubstituted arylaminoalkyl groups, substituted or unsubstituted diarylaminoalkyl groups, substituted or unsubstituted (alkyl)(aryl)aminoalkyl groups, substituted or unsubstituted heterocyclylalkyl groups, substituted or unsubstituted aminoalkyl groups, substituted or unsubstituted heterocyclylaminoalkyl groups, substituted and unsubstituted diheterocyclylaminoalkyl groups, substituted and unsubstituted (alkyl)(heterocyclyl)aminoalkyl groups, substituted and unsubstituted (aryl)(heterocyclyl)aminoalkyl groups, substituted or unsubstituted hydroxyalkyl groups, substituted or unsubstituted alkoxyalkyl groups, substituted or unsubstituted aryloxyalkyl groups, or substituted or unsubstituted heterocycloxyalkyl groups. R^4 and R^5 may join to form a 5 to 7 membered substituted or unsubstituted carbocyclic or heterocyclic ring. Similarly, R^5 and R^6 may join to form a 5 to 7 membered substituted or unsubstituted carbocyclic or heterocyclic ring. Finally, R^6 and R^7 may also join to form a 5 to 7 membered substituted or unsubstituted carbocyclic or heterocyclic ring.
- In one group of preferred compounds of structure I, R^4 , R^5 , R^6 , and R^7 are all H. In other more preferred compounds of structure I, R^5 , R^6 or both R^5 and R^6 are alkyl groups having from one to four carbon atoms. In still other preferred compounds having the formula of structure I, R^5 or R^6 is an $-OR^{14}$ group and R^{14} is an alkyl, aryl, heterocyclyl, or heterocyclylalkyl group. In still further preferred compounds of structure I, R^5 or R^6 is a $-OCH_2(CH_2)_q(\text{heterocyclyl})$ group where q is 0, 1, 2, 3, or 4. More preferably the heterocyclyl group of the $-OCH_2(CH_2)_q(\text{heterocyclyl})$ group is a heterocycle selected from substituted or unsubstituted morpholine, substituted or unsubstituted piperazine, substituted or unsubstituted piperidine, substituted or unsubstituted pyrrolidine, substituted or unsubstituted pyrrole, substituted or unsubstituted imidazole, substituted or

WO 02/18383

PCT/US01/41942

-35-

unsubstituted pyrazole, substituted or unsubstituted 1,2,3-triazole, substituted or unsubstituted 1,2,4-triazole, substituted or unsubstituted tetrazole, substituted or unsubstituted thiomorpholine, substituted or unsubstituted homopiperazine, substituted or unsubstituted oxazolidin-2-one, substituted or unsubstituted

5 pyrrolidin-2-one, substituted or unsubstituted pyridine, substituted or unsubstituted oxazole, substituted or unsubstituted isoxazole, substituted or unsubstituted thiazole, substituted or unsubstituted isothiazole, substituted or unsubstituted furan, substituted or unsubstituted thiophene, substituted or unsubstituted tetrahydrofuran, substituted or unsubstituted tetrahydrothiophene, substituted or unsubstituted

10 benzimidazole, substituted or unsubstituted benzoxazole, or substituted or unsubstituted benzothiazole.

In still other preferred compounds having the structure I, at least one of R⁴, R⁵, R⁶, or R⁷ is a substituted or unsubstituted heterocyclyl group, more specifically a substituted or unsubstituted heterocyclyl group comprising at least one

15 O or N atom, and more particularly a substituted or unsubstituted heterocyclyl group selected from morpholine, piperazine, piperidine, 1,2,3-triazole, 1,2,4-triazole, tetrazole, pyrrolidine, pyrazole, pyrrole, thiomorpholine, homopiperazine, benzimidazole, oxazolidin-2-one, pyrrolidin-2-one, imidazole, isoxazole, oxazole, isothiazole, thiazole, thiophene, furan, pyran, tetrahydrothiophene, tetrahydrofuran,

20 tetrahydropyran, and pyridine.

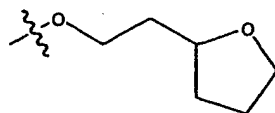
In groups including heterocyclyl groups, the heterocycle may be attached in various ways. For example in the -OCH₂(CH₂)_q(heterocyclyl) group, the heterocyclyl group may be bonded to a methylene carbon of the -OCH₂(CH₂)_q group of the -OCH₂(CH₂)_q(heterocyclyl) group through various ring members. By

25 way of non-limiting example, where q is 1 and the heterocyclyl group is tetrahydrofuran, the group could be represented by the formula -OCH₂CH₂-(tetrahydrofuranyl) which corresponds to the following two structures:

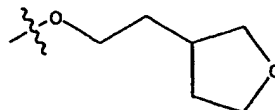
WO 02/18383

PCT/US01/41942

-36-



IV

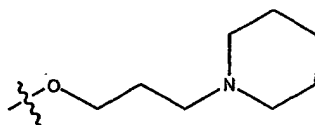


V

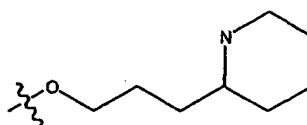
where structure IV represents the group that can be referred to as the $-\text{OCH}_2\text{CH}_2(2\text{-tetrahydrofuranyl})$ group and structure V represents the group that can be referred to as the $-\text{OCH}_2\text{CH}_2(3\text{-tetrahydrofuranyl})$ group. When the heterocyclyl group is a

5 N-containing heterocycle, such as, but not limited to piperidine, piperazine, morpholine, or pyrrolidine, the heterocycle can be bonded to the methylene carbon through a ring carbon atom or through a nitrogen atom in the ring of the N-containing heterocycle. Both of these are preferred. Where the heterocyclyl group is a piperidine and q is 2 for a $-\text{OCH}_2(\text{CH}_2)_q(\text{heterocyclyl})$ group, the following

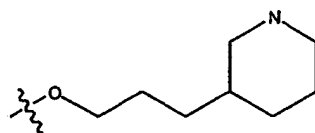
10 structures are possible and preferred:



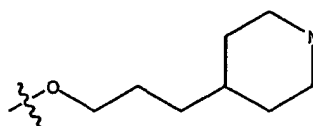
VI



VII



VIII



IX

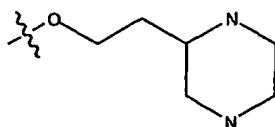
Structure VI is an example of a $-\text{O}(\text{CH}_2)_3(\text{N-piperidinyl})$ or $-\text{O}(\text{CH}_2)_3(1\text{-piperidinyl})$ group. Structure VII is an example of a $-\text{O}(\text{CH}_2)_3(2\text{-piperidinyl})$ group. Structure VIII is an example of a $-\text{O}(\text{CH}_2)_3(3\text{-piperidinyl})$ group. Structure IX is an example of a $-\text{O}(\text{CH}_2)_3(4\text{-piperidinyl})$ group. Where the

15 heterocyclyl group is a piperazine and q is 1 for an $-\text{OCH}_2(\text{CH}_2)_q(\text{heterocyclyl})$ group, the following structures are possible and preferred:

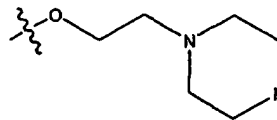
WO 02/18383

PCT/US01/41942

-37-



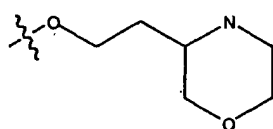
X



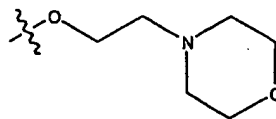
XI

Structure X is an example of a $-\text{O}(\text{CH}_2)_2(2\text{-piperazinyl})$ group, and structure XI is an example of a $-\text{O}(\text{CH}_2)_2(1\text{-piperazinyl})$ or $-\text{O}(\text{CH}_2)_2(\text{N-piperazinyl})$ group. Where the heterocyclyl group is a morpholine and q is 1 for an

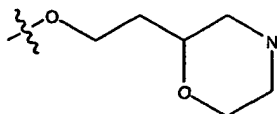
5 $-\text{OCH}_2(\text{CH}_2)_q(\text{heterocyclyl})$ group, the following structures are possible and preferred:



XII



XIII



XIV

Structure XII is an example of a $-\text{O}(\text{CH}_2)_2(3\text{-morpholinyl})$ group, structure XIII is an example of a $-\text{O}(\text{CH}_2)_2(4\text{-morpholinyl})$ or $-\text{O}(\text{CH}_2)_2(\text{N-morpholinyl})$ group, and structure XIV is an example of a $-\text{O}(\text{CH}_2)_2(2\text{-morpholinyl})$ group. It will be observed that where the group is a pyrrolidine, and q is 1, the

10 structures available include $-\text{O}(\text{CH}_2)_2(1\text{-pyrrolidinyl})$ or $-\text{O}(\text{CH}_2)_2(\text{N-pyrrolidinyl})$, $-\text{O}(\text{CH}_2)_2(2\text{-pyrrolidinyl})$, and $-\text{O}(\text{CH}_2)_2(3\text{-pyrrolidinyl})$.

In compounds of structure I, R^8 may be a substituted or unsubstituted

15 alkyl group, a substituted or unsubstituted aryl group, a substituted or unsubstituted heterocyclyl group, a substituted or unsubstituted heterocyclalkyl group, $-\text{C}(=\text{O})\text{H}$, a $-\text{C}(=\text{O})$ -alkyl group, a $-\text{C}(=\text{O})$ -aryl group, a $-\text{C}(=\text{O})\text{O}$ -alkyl group, a $-\text{C}(=\text{O})\text{O}$ -aryl group, $-\text{C}(=\text{O})\text{NH}_2$, a $-\text{C}(=\text{O})\text{NH}(\text{alkyl})$ group, a $-\text{C}(=\text{O})\text{NH}(\text{aryl})$

WO 02/18383

PCT/US01/41942

-38-

- group, a $-C(=O)N(alkyl)_2$ group, a $-C(=O)N(aryl)_2$ group, a $-C(=O)N(alkyl)(aryl)$ group, $-NH_2$, a $-NH(alkyl)$ group, a $-NH(aryl)$ group, a $-N(alkyl)_2$ group, a $-N(alkyl)(aryl)$ group, a $-N(aryl)_2$ group, a $-C(=O)NH(heterocyclyl)$ group, a $-C(=O)N(heterocyclyl)_2$ group, a $-C(=O)N(alkyl)(heterocyclyl)$ group, or a
- 5 $-C(=O)N(aryl)(heterocyclyl)$ group.

R^9 and R^{18} may be the same or different in compounds of structure I and are independently selected from substituted or unsubstituted alkyl groups, or substituted or unsubstituted aryl groups.

- In compounds of structure I, R^{10} is selected from H, substituted or
- 10 unsubstituted alkyl groups, substituted or unsubstituted aryl groups, or substituted or unsubstituted heterocyclyl groups, and R^{11} is selected from H, substituted or unsubstituted alkyl groups, substituted or unsubstituted aryl groups, substituted or unsubstituted heterocyclyl groups, $-OH$, alkoxy groups, aryloxy groups, $-NH_2$, substituted or unsubstituted heterocyclylalkyl groups, substituted or unsubstituted
- 15 aminoalkyl groups, substituted or unsubstituted alkylaminoalkyl groups, substituted or unsubstituted dialkylaminoalkyl groups, substituted or unsubstituted arylaminoalkyl groups, substituted or unsubstituted diarylaminoalkyl groups, substituted or unsubstituted (alkyl)(aryl)aminoalkyl groups, substituted or unsubstituted alkylamino groups, substituted or unsubstituted arylamino groups,
- 20 substituted or unsubstituted dialkylamino groups, substituted or unsubstituted diarylamino groups, substituted or unsubstituted (alkyl)(aryl)amino groups, $-C(=O)H$, $-C(=O)-alkyl$ groups, $-C(=O)-aryl$ groups, $-C(=O)O-alkyl$ groups, $-C(=O)O-aryl$ groups, $-C(=O)NH_2$, $-C(=O)NH(alkyl)$ groups, $-C(=O)NH(aryl)$ groups, $-C(=O)N(alkyl)_2$ groups, $-C(=O)N(aryl)_2$ groups, $-C(=O)N(alkyl)(aryl)$
- 25 groups, $-C(=O)-heterocyclyl$ groups, $-C(=O)-O-heterocyclyl$ groups, $-C(=O)NH(heterocyclyl)$ groups, $-C(=O)-N(heterocyclyl)_2$ groups, $-C(=O)-N(alkyl)(heterocyclyl)$ groups, $-C(=O)-N(aryl)(heterocyclyl)$ groups, substituted or unsubstituted heterocyclylaminoalkyl groups, substituted and unsubstituted diheterocyclylaminoalkyl groups, substituted and unsubstituted

WO 02/18383

PCT/US01/41942

-39-

(alkyl)(heterocyclyl)aminoalkyl groups, substituted and unsubstituted
(aryl)(heterocyclyl)aminoalkyl groups, substituted or unsubstituted hydroxyalkyl
groups, substituted or unsubstituted alkoxyalkyl groups, substituted or unsubstituted
aryloxyalkyl groups, or substituted or unsubstituted heterocyclyloxyalkyl groups.

- 5 R¹⁰ and R¹¹ may join together to form a 5 to 7 membered saturated or unsaturated,
substituted or unsubstituted N-containing ring.

- In compounds of structure I, R¹² is selected from H, -OH, alkoxy
groups, aryloxy groups, -NH₂, -NH(alkyl) groups, -NH(aryl) groups, -N(alkyl)₂
groups, -N(aryl)₂ groups, -N(alkyl)(aryl) groups, substituted or unsubstituted alkyl
10 groups, substituted or unsubstituted aryl groups, -NH(heterocyclyl) groups,
-N(heterocyclyl)₂ groups, -N(alkyl)(heterocyclyl) groups, or -N(aryl)(heterocyclyl)
groups.

- In structure I, R¹⁴ is selected from substituted or unsubstituted alkyl
groups, substituted or unsubstituted aryl groups, substituted or unsubstituted
15 heterocyclyl groups, substituted or unsubstituted heterocyclylalkyl groups,
-C(=O)H, -C(=O)-alkyl groups, -C(=O)-aryl groups, -C(=O)-heterocyclyl
groups, -C(=O)NH₂, -C(=O)NH(alkyl) groups, -C(=O)NH(aryl) groups,
-C(=O)N(alkyl)₂ groups, -C(=O)N(aryl)₂ groups, -C(=O)N(alkyl)(aryl) groups,
-C(=O)NH-heterocyclyl groups, -C(=O)N-(heterocyclyl)₂ groups,
20 -C(=O)N(alkyl)(heterocyclyl) groups, -C(=O)N(aryl)(heterocyclyl) groups,
substituted or unsubstituted aminoalkyl groups, substituted or unsubstituted
alkylaminoalkyl groups, substituted or unsubstituted dialkylaminoalkyl groups,
substituted or unsubstituted arylaminoalkyl groups, substituted or unsubstituted
diarylaminominoalkyl groups, substituted or unsubstituted (alkyl)(aryl)aminoalkyl
25 groups, substituted or unsubstituted heterocyclylaminoalkyl groups, substituted or
unsubstituted diheterocyclylaminoalkyl groups, substituted or unsubstituted
(heterocyclyl)(alkyl)aminoalkyl groups, substituted or unsubstituted
(heterocyclyl)(aryl)aminoalkyl groups, substituted or unsubstituted alkoxyalkyl
groups, substituted or unsubstituted aryloxyalkyl groups, substituted or

WO 02/18383

PCT/US01/41942

-40-

unsubstituted hydroxyalkyl groups, or substituted or unsubstituted heterocycloxyalkyl groups.

- In compounds of structure I, R¹⁵ is selected from H, substituted or unsubstituted alkyl groups, substituted or unsubstituted aryl groups, or substituted or unsubstituted heterocyclyl groups. R¹⁶ is selected from H, substituted or unsubstituted alkyl groups, substituted or unsubstituted aryl groups, substituted or unsubstituted heterocyclyl groups, -C(=O)H, -C(=O)-alkyl groups, -C(=O)-aryl groups, -C(=O)NH₂, -C(=O)NH(alkyl) groups, -C(=O)NH(aryl) groups, -C(=O)N(alkyl)₂ groups, -C(=O)N(aryl)₂ groups, -C(=O)N(alkyl)(aryl) groups, -C(=O)O-alkyl groups, -C(=O)O-aryl groups, substituted or unsubstituted aminoalkyl groups, substituted or unsubstituted alkylaminoalkyl groups, substituted or unsubstituted dialkylaminoalkyl groups, substituted or unsubstituted arylaminoalkyl groups, substituted or unsubstituted diarylaminoalkyl groups, substituted or unsubstituted (alkyl)(aryl)aminoalkyl groups, substituted or unsubstituted heterocyclylalkyl groups, -C(=O)-heterocyclyl groups, -C(=O)-O-heterocyclyl groups, -C(=O)NH(heterocyclyl) groups, -C(=O)-N(heterocyclyl)₂ groups, -C(=O)-N(alkyl)(heterocyclyl) groups, -C(=O)-N(aryl)(heterocyclyl) groups, substituted or unsubstituted heterocyclylaminoalkyl groups, substituted and unsubstituted diheterocyclylaminoalkyl groups, substituted and unsubstituted (heterocyclyl)(alkyl)aminoalkyl groups, substituted and unsubstituted (heterocyclyl)(aryl)aminoalkyl groups, substituted or unsubstituted hydroxyalkyl groups, substituted or unsubstituted alkoxyalkyl groups, substituted or unsubstituted aryloxyalkyl groups, or substituted or unsubstituted heterocycloxyalkyl groups.
- R¹⁵ and R¹⁶ may join together to form a 5 to 7 membered saturated or unsaturated, substituted or unsubstituted N-containing ring.

R¹⁷, R¹⁹, and R²⁰ may be the same or different and are independently selected from H, -NH₂, -NH(alkyl) groups, -NH(aryl) groups, -N(alkyl)₂ groups, -N(aryl)₂ groups, -N(alkyl)(aryl) groups, -NH(heterocyclyl) groups,

WO 02/18383

PCT/US01/41942

-41-

-N(heterocyclyl)(alkyl) groups, -N(heterocyclyl)(aryl) groups, -N(heterocyclyl)₂ groups, substituted and unsubstituted alkyl groups, substituted and unsubstituted aryl groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted aryloxy groups, heterocyclyloxy groups, -NHOH, -N(alkyl)OH groups, -N(aryl)OH groups, -N(alkyl)O-alkyl groups, -N(aryl)O-alkyl groups, -N(alkyl)O-aryl groups, and -N(aryl)O-aryl groups.

In some preferred compounds of structure I, R¹⁷ is selected from unsubstituted alkyl groups, substituted or unsubstituted aryl groups, -NH₂, -NH(alkyl) groups, -N(alkyl)₂ groups, -NH(aryl) groups, -N(aryl)₂ groups, -N(alkyl)(aryl) groups, -NH(heterocyclyl) groups, -N(heterocyclyl)(alkyl) groups, -N(heterocyclyl)(aryl) groups, -N(heterocyclyl)₂ groups, or N-containing heterocycles, and the N-containing heterocycles are bonded to the carbonyl carbon of the -C(=O)-R¹⁷ group through either a nitrogen atom or a carbon atom in the rings of the N-containing heterocycles. In still more preferred compounds in which R¹⁷ is a N-containing heterocycle, the N-containing heterocycle of the R¹⁷ group is selected from substituted or unsubstituted morpholine, substituted or unsubstituted pyrrolidine, substituted or unsubstituted piperazine, substituted or unsubstituted piperidine, substituted or unsubstituted pyrrole, substituted or unsubstituted imidazole, substituted or unsubstituted pyrazole, substituted or unsubstituted 1,2,3-triazole, substituted or unsubstituted 1,2,4-triazole, substituted or unsubstituted tetrazole, substituted or unsubstituted thiomorpholine, substituted or unsubstituted homopiperazine, substituted or unsubstituted oxazolidin-2-one, substituted or unsubstituted pyrrolidin-2-one, substituted or unsubstituted pyridine, substituted or unsubstituted oxazole, substituted or unsubstituted isoxazole, substituted or unsubstituted thiazole, substituted or unsubstituted isothiazole, substituted or unsubstituted benzimidazole, substituted or unsubstituted benzoxazole, or substituted or unsubstituted benzothiazole.

WO 02/18383

PCT/US01/41942

-42-

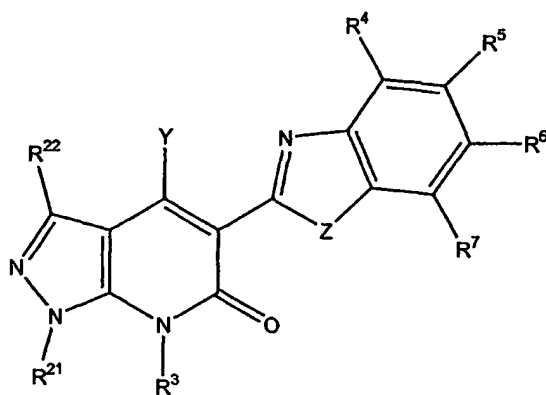
In other preferred compounds having structure I, R¹⁴ or R¹⁶ is selected from substituted or unsubstituted aminoalkyl groups, substituted or unsubstituted alkylaminoalkyl groups, substituted or unsubstituted arylaminoalkyl groups, substituted or unsubstituted dialkylaminoalkyl groups, substituted or unsubstituted diarylaminoalkyl groups, alkylaryl aminoalkyl groups, or substituted or unsubstituted heterocyclalkyl groups, including: -CH₂(CH₂)_pNH₂ groups, -CH₂(CH₂)_pNH(alkyl) groups, -CH₂(CH₂)_pNH(aryl) groups, -CH₂(CH₂)_pN(alkyl)₂ groups, -CH₂(CH₂)_pN(aryl)₂ groups, -CH₂(CH₂)_pN(alkyl)(aryl) groups, or -CH₂(CH₂)_p(heterocyclyl) groups, where p is an integer ranging from 0 to 4 and the heterocyclyl group of the -CH₂(CH₂)_p(heterocyclyl) group is a N-containing heterocycle selected from substituted or unsubstituted morpholine, substituted or unsubstituted pyrrolidine, substituted or unsubstituted piperazine, substituted or unsubstituted piperidine, substituted or unsubstituted pyrrole, substituted or unsubstituted imidazole, substituted or unsubstituted pyrazole, substituted or unsubstituted 1,2,3-triazole, substituted or unsubstituted 1,2,4-triazole, substituted or unsubstituted tetrazole, substituted or unsubstituted thiomorpholine, substituted or unsubstituted homopiperazine, substituted or unsubstituted oxazolidin-2-one, substituted or unsubstituted pyrrolidin-2-one, substituted or unsubstituted pyridine, substituted or unsubstituted oxazole, substituted or unsubstituted isoxazole, substituted or unsubstituted thiazole, substituted or unsubstituted isothiazole, substituted or unsubstituted benzimidazole, substituted or unsubstituted benzoxazole, or substituted or unsubstituted benzothiazole.

Other compounds having the structure I are provided that also have the structure IA. These are compounds in which R¹ and R² of structure I join together to form a 5 membered ring having having two N atoms.

WO 02/18383

PCT/US01/41942

-43-



IA

- In compounds of structure IA, R^{21} is selected from H or substituted or unsubstituted alkyl groups; R^{22} may be the same or different from R^4 , R^5 , R^6 , R^7 and is independently selected from H, Cl, Br, F, I, $-\text{NO}_2$, $-\text{CN}$, $-\text{OH}$, $-\text{OR}^{14}$ groups, $-\text{NR}^{15}\text{R}^{16}$ groups, $-\text{C}(=\text{O})\text{R}^{17}$ groups, $-\text{SH}$, $-\text{SR}^{18}$ groups, $-\text{S}(=\text{O})\text{R}^{19}$ groups, $\text{S}(=\text{O})_2\text{R}^{20}$ groups, substituted or unsubstituted amidinyl groups, substituted or unsubstituted guanidinyl groups, substituted or unsubstituted primary, secondary, or tertiary alkyl groups, substituted or unsubstituted aryl groups, substituted or unsubstituted alkenyl groups, substituted or unsubstituted alkynyl groups, substituted or unsubstituted heterocyclyl groups, substituted or unsubstituted alkylaminoalkyl groups, substituted or unsubstituted dialkylaminoalkyl groups, substituted or unsubstituted arylaminoalkyl groups, substituted or unsubstituted diarylaminoalkyl groups, substituted or unsubstituted (alkyl)(aryl)aminoalkyl groups, substituted or unsubstituted heterocyclylalkyl groups, substituted or unsubstituted aminoalkyl groups, substituted or unsubstituted heterocyclylaminoalkyl groups, substituted or unsubstituted hydroxyalkyl groups, substituted or unsubstituted alkoxyalkyl groups, substituted or unsubstituted aryloxyalkyl groups, or substituted or unsubstituted heterocycloxyalkyl groups; and R^3 through R^{21} have the values described above with respect to compounds of structure I.

WO 02/18383

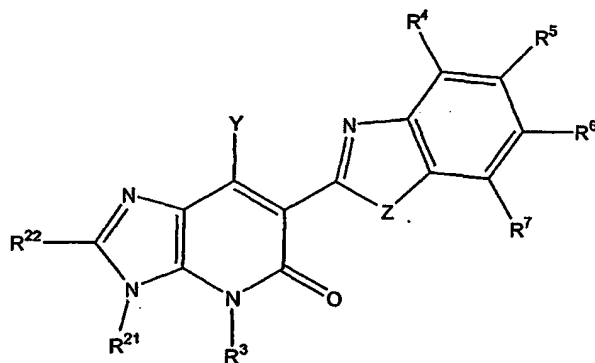
PCT/US01/41942

-44-

Other compounds of structure IA are those in which Z is an NR^{13} and more preferably where R^{13} is H. Other compounds of structure IA are provided in which R^3 is H.

Still other compounds of structure IA are those in which Y is an
 5 $-\text{NR}^{10}\text{R}^{11}$ group. In still other compounds of structure IA, Y is an $-\text{NR}^{10}\text{R}^{11}$ group and R^{10} and R^{11} are hydrogen atoms.

Still other compounds having the structure I are provided that have the structure IB. Like compounds of structure IA, these are compounds in which R^1 and R^2 of structure I join together to form a 5 membered ring having having two N
 10 atoms.



IB

In compounds of structure IB, R^{21} is selected from H or substituted or unsubstituted alkyl groups; R^{22} may be the same or different from R^4 , R^5 , R^6 , R^7 and is independently selected from H, Cl, Br, F, I, $-\text{NO}_2$, $-\text{CN}$, $-\text{OH}$, $-\text{OR}^{14}$ groups,
 15 $-\text{NR}^{15}\text{R}^{16}$ groups, $-\text{C}(=\text{O})\text{R}^{17}$ groups, $-\text{SH}$, $-\text{SR}^{18}$ groups, $-\text{S}(=\text{O})\text{R}^{19}$ groups, $\text{S}(=\text{O})_2\text{R}^{20}$ groups, substituted or unsubstituted amidinyl groups, substituted or unsubstituted guanidinyl groups, substituted or unsubstituted primary, secondary, or tertiary alkyl groups, substituted or unsubstituted aryl groups, substituted or unsubstituted alkenyl groups, substituted or unsubstituted alkynyl groups,
 20 substituted or unsubstituted heterocyclyl groups, substituted or unsubstituted

WO 02/18383

PCT/US01/41942

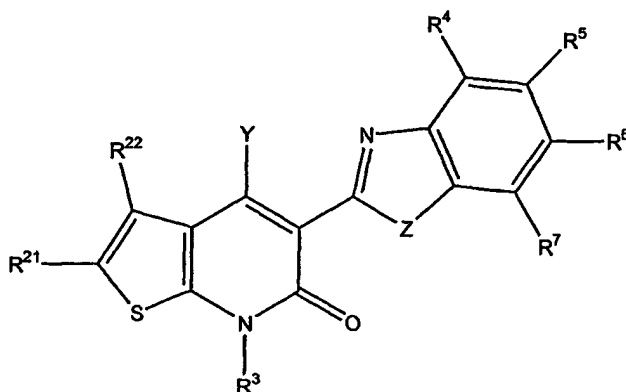
-45-

alkylaminoalkyl groups, substituted or unsubstituted dialkylaminoalkyl groups, substituted or unsubstituted arylaminoalkyl groups, substituted or unsubstituted diarylaminoalkyl groups, substituted or unsubstituted (alkyl)(aryl)aminoalkyl groups, substituted or unsubstituted heterocyclalkyl groups, substituted or unsubstituted aminoalkyl groups, substituted or unsubstituted heterocyclaminoalkyl groups, substituted or unsubstituted hydroxyalkyl groups, substituted or unsubstituted alkoxyalkyl groups, substituted or unsubstituted aryloxyalkyl groups, or substituted or unsubstituted heterocycloxyalkyl groups; and R^3 through R^{21} have the values described above with respect to compounds of structure I.

Other compounds of structure IB include those in which Z is an NR^{13} and more preferably those where R^{13} is H. Other compounds of structure IB are those in which R^3 is H.

Still other compounds of structure IB are those in which Y is an $-NR^{10}R^{11}$ group. In still other compounds of structure IB, Y is an $-NR^{10}R^{11}$ group and R^{10} and R^{11} are hydrogen atoms.

Still other compounds having the structure I are provided that have the structure IC. These are compounds in which R^1 and R^2 of structure I join together to form a 5 membered ring having one S atom.



IC

WO 02/18383

PCT/US01/41942

-46-

In compounds of structure IC, R^{21} and R^{22} may be the same or different from R^4 , R^5 , R^6 , R^7 and each other and are independently selected from H, Cl, Br, F, I, $-NO_2$, $-CN$, $-OH$, $-OR^{14}$ groups, $-NR^{15}R^{16}$ groups, $-C(=O)R^{17}$ groups, $-SH$, $-SR^{18}$ groups, $-S(=O)R^{19}$ groups, $S(=O)_2R^{20}$ groups, substituted or

5 unsubstituted amidinyl groups, substituted or unsubstituted guanidinyl groups, substituted or unsubstituted primary, secondary, or tertiary alkyl groups, substituted or unsubstituted aryl groups, substituted or unsubstituted alkenyl groups, substituted or unsubstituted alkynyl groups, substituted or unsubstituted heterocyclyl groups, substituted or unsubstituted alkylaminoalkyl groups, substituted or unsubstituted

10 dialkylaminoalkyl groups, substituted or unsubstituted arylaminoalkyl groups, substituted or unsubstituted diarylaminoalkyl groups, substituted or unsubstituted (alkyl)(aryl)aminoalkyl groups, substituted or unsubstituted heterocyclylalkyl groups, substituted or unsubstituted aminoalkyl groups, substituted or unsubstituted heterocyclylaminoalkyl groups, substituted or unsubstituted hydroxyalkyl groups,

15 substituted or unsubstituted alkoxyalkyl groups, substituted or unsubstituted aryloxyalkyl groups, or substituted or unsubstituted heterocycliloxyalkyl groups; and R^3 through R^{20} have the values described above with respect to compounds of structure I.

Other compounds of structure IC are those in which Z is an NR^{13} and

20 more preferably those where R^{13} is H. Other compounds of structure IC are those in which R^3 is H.

Still other compounds of structure IC are those in which Y is an $-NR^{10}R^{11}$ group. In still other compounds of structure IC, Y is an $-NR^{10}R^{11}$ group and R^{10} and R^{11} are hydrogen atoms.

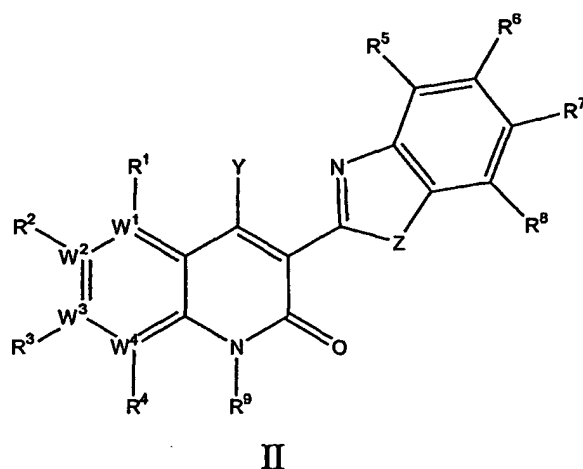
25 Particularly preferred inhibitors of VEGF-RTK are compounds having the structure II, tautomers of the compounds, pharmaceutically acceptable salts of the compounds, and pharmaceutically acceptable salts of the tautomers. These are compounds having a ring system similar to that of Structure I where R^1 and R^2 , as defined above with respect to Structure I, join together to form a 6

WO 02/18383

PCT/US01/41942

-47-

membered ring that includes at least one N atom. Structure II has the following formula:



In compounds of structure II, W^1 , W^2 , W^3 , and W^4 are selected from C or N, and at least one of W^1 , W^2 , W^3 , or W^4 is N. In some preferred compounds of structure II, W^1 is N and R^1 is absent or H. In other preferred compounds of structure II, W^2 is N and R^2 is absent or H. In still other preferred compounds of structure II, W^3 is N and R^3 is absent or H. In yet other preferred compounds of structure II, W^4 is N and R^4 is absent or H. In some preferred compounds of structure II, one of W^1 , W^2 , W^3 , and W^4 is N. In other preferred compounds of structure II, two of W^1 , W^2 , W^3 , and W^4 are N. In yet other preferred embodiments, W^1 , W^2 , and W^3 are all C and W^4 is N; W^1 , W^2 , and W^4 are all C and W^3 is N; W^1 , W^3 , and W^4 are all C and W^2 is N; or W^2 , W^3 , and W^4 are all C and W^1 is N.

In compounds having structure II, Y is selected from $-OH$, $-OR^{10}$ groups, $-SH$, $-SR^{11}$ groups, $-NR^{12}R^{13}$ groups, $-CN$, $-C(=O)-R^{14}$ groups, substituted or unsubstituted alkyl groups, substituted or unsubstituted alkenyl groups, substituted or unsubstituted alkynyl groups, substituted or unsubstituted aralkyl groups, substituted or unsubstituted heterocyclalkyl groups, substituted or unsubstituted alkylaminoalkyl groups, substituted or unsubstituted dialkylaminoalkyl

WO 02/18383

PCT/US01/41942

-48-

groups, substituted or unsubstituted arylaminoalkyl groups, substituted or unsubstituted diarylaminoalkyl groups, substituted or unsubstituted (alkyl)(aryl)aminoalkyl groups, substituted or unsubstituted heterocyclylaminoalkyl groups, substituted and unsubstituted diheterocyclylaminoalkyl groups, substituted and unsubstituted (heterocyclyl)(alkyl)aminoalkyl groups, substituted and unsubstituted (heterocyclyl)(aryl)aminoalkyl groups, substituted or unsubstituted heterocyclyl groups, substituted or unsubstituted aryl groups, substituted or unsubstituted hydroxyalkyl groups, substituted or unsubstituted alkoxyalkyl groups, substituted or unsubstituted aryloxyalkyl groups, or substituted or unsubstituted heterocyclyloxyalkyl groups.

In preferred compounds of structure II, Y is selected from -OH, -OR¹⁰ groups, or -NR¹²R¹³ groups, or more preferably -NR¹²R¹³ groups, or still more preferably -NR¹²R¹³ groups where one or both of R¹² and R¹³ are H. In other preferred compounds having the structure II, Y is selected from -N(CH₃)₂, -NH(CH₃), -NH(CH₂CH₃), -N(CH₂CH₃)₂, -NH(aryl) groups, -N(aryl)₂ groups, -NHNH₂, -NHN(CH₃)₂, -N(CH₃)NH(CH₃), -NH(CH₂)_mNH₂ groups, -NH(CH₂)_mNH(alkyl) groups, -NH(CH₂)_mN(alkyl)₂ groups, -N(alkyl)(CH₂)_mNH₂ groups, -N(alkyl)(CH₂)_mNH(alkyl) groups, -N(alkyl)(CH₂)_mN(alkyl)₂ groups, -NH(CH₂)_n(heterocyclyl) groups, -N(alkyl)[(CH₂)_n(heterocyclyl)] groups, -NH(CH₂)_mOH groups, -NH(CH₂)_mOCH₃ groups, -NHCH₂CH(NH₂)CH(CH₃)₂, -NH(2-aminocyclohexyl), -NH(cyclohexyl), -NHOCCH₃, -NH(N-morpholinyl), -NH(quinuclidyl), especially -NH(quinuclid-3-yl), and groups where R¹² and R¹³ join to form a substituted or unsubstituted saturated 5 or 6 membered N-containing ring, where m is 2, 3, or 4 and n is 0, 1, 2, or 3. Still more preferred compounds of this type are those in which Y is selected from -NH(5-benzimidazolyl), -NH(CH₂)₂N(CH₃)₂, -NH(CH₂)₂OH, -NH(CH₂)(4-imidazolyl), -NH(CH₂)(3-imidazolyl), -NH(CH₂)(4-pyridyl), -NH(CH₂)(2-pyridyl), -NH(CH₂)(3-pyridyl), -NH(CH₂)(2-tetrahydrofuranyl), -NH(CH₂)(4-piperidinyl), -NH(CH₂)(3-piperidinyl), -NH(CH₂)₂[2-(N-methyl-pyrrolidinyl)], -NH(CH₂)₂(2-pyrrolidinyl),

WO 02/18383

PCT/US01/41942

-49-

-NH(CH₂)[2-(N-methylpyrrolidinyl)], -NH(CH₂)(2-pyrrolidinyl), -NH(3-piperidinyl), or -NH(3-pyrrolidinyl).

In compound of structure II, Z is O, S, and NR¹⁵ groups. In preferred compounds of structure II, Z is an NR¹⁵ group or more preferably is an NR¹⁵ group where R¹⁵ is H.

In compounds of structure II, R¹, R², R³, R⁴, R⁵, R⁶, R⁷, and R⁸ may be the same or different and are independently selected from H, Cl, Br, F, I, -NO₂, -CN, -OH, -OR¹⁶ groups, -NR¹⁷R¹⁸ groups, -C(=O)R¹⁹ groups, -SH, -SR²⁰ groups, -S(=O)R²¹ groups, S(=O)₂R²² groups, substituted or unsubstituted amidinyl groups, substituted or unsubstituted guanidinyl groups, substituted or unsubstituted primary, secondary, or tertiary alkyl groups, substituted or unsubstituted aryl groups, substituted or unsubstituted alkenyl groups, substituted or unsubstituted alkynyl groups, substituted or unsubstituted heterocyclyl groups, substituted or unsubstituted alkylaminoalkyl groups, substituted or unsubstituted dialkylaminoalkyl groups, substituted or unsubstituted arylaminoalkyl groups, substituted or unsubstituted diarylaminoalkyl groups, substituted or unsubstituted (alkyl)(aryl)aminoalkyl groups, substituted or unsubstituted heterocyclylalkyl groups, substituted or unsubstituted aminoalkyl groups, substituted or unsubstituted heterocyclylaminoalkyl groups, substituted and unsubstituted diheterocyclylaminoalkyl groups, substituted and unsubstituted (alkyl)(heterocyclyl)aminoalkyl groups, substituted and unsubstituted (aryl)(heterocyclyl)aminoalkyl groups, substituted or unsubstituted hydroxyalkyl groups, substituted or unsubstituted alkoxyalkyl groups, substituted or unsubstituted aryloxyalkyl groups, or substituted or unsubstituted heterocycloxyalkyl groups, and R¹ is absent or H if W¹ is N, R² is absent or H if W² is N, R³ is absent or H if W³ is N, and R⁴ is absent or H if W⁴ is N.

Some preferred compounds have the structure II where at least one of R¹, R², R³, R⁴, R⁵, R⁶, R⁷, or R⁸ is a substituted or unsubstituted heterocyclyl group, and in more preferred embodiments, a substituted or unsubstituted

WO 02/18383

PCT/US01/41942

-50-

heterocyclyl group selected from morpholine, piperazine, piperidine, 1,2,3-triazole, 1,2,4-triazole, tetrazole, pyrrolidine, pyrazole, pyrrole, thiomorpholine, homopiperazine, benzimidazole, oxazolidin-2-one, pyrrolidin-2-one, imidazole, isothiazole, thiazole, thiophene, furan, pyran, tetrahydrothiophene, tetrahydrofuran, 5 tetrahydropyran, and pyridine.

Still other preferred compounds having structure II are those in which R¹, R², and R³ are H, and W⁴ is N. Still other compounds having the formula of structure II are provided in which R², R³, and R⁴ are H, and W¹ is N. Still other compounds having the formula of structure II are provided in which R¹, 10 R³, and R⁴ are H, and W² is N. Still other compounds having the formula of structure II are provided in which R¹, R², and R⁴ are H, and W³ is N.

In other preferred compounds, R¹ or R² is selected from F, Cl, substituted or unsubstituted alkoxy groups, substituted or unsubstituted heterocyclyloxy groups, substituted or unsubstituted heterocyclylalkoxy groups, 15 substituted or unsubstituted heterocyclyl groups, substituted or unsubstituted alkyl-, heterocycyl-, or aryl-aminoalkyl groups, substituted or unsubstituted dialkyl- or diaryl-aminoalkyl groups, substituted or unsubstituted alkylaryl-aminoalkyl groups, substituted or unsubstituted alkyl- and aryl-aminoalkoxy groups, substituted or unsubstituted dialkyl- and diaryl-aminoalkoxy groups, or substituted or 20 unsubstituted alkylaryl-aminoalkoxy groups. Particular examples include: -C(=O)N(alkyl)₂ groups, -OCH₂CH₂(N-morpholinyl), N-morpholinyl, -OCH₂CH₂N(alkyl)₂ groups, -OCH₂CH₂NH(alkyl) groups, -OCH₂CH₂NH₂, -OCH₂CH₂NH(aryl) groups, -OCH₂CH₂N(aryl)₂ groups, alkoxy groups, -OCH₂CH₂N(alkyl)(aryl) groups, -O(4-piperidinyl), -O[4-(1-alkyl)piperidinyl] 25 groups, -OCH₂(2-pyridyl), -O(3-pyrrolidinyl), or -O[3-(1-alkyl)pyrrolidinyl] groups.

Still other preferred compounds include those in which R² is selected from F, Cl, -NO₂, substituted or unsubstituted alkoxy groups, substituted or unsubstituted heterocyclylalkoxy groups, substituted or unsubstituted heterocyclyl

WO 02/18383

PCT/US01/41942

-51-

groups, substituted or unsubstituted alkyl-, heterocycl-, or aryl-aminoalkyl groups, substituted or unsubstituted dialkyl- and diaryl-aminoalkyl groups, substituted or unsubstituted alkylarylaminoalkyl groups, substituted or unsubstituted alkyl- and aryl-aminoalkoxy groups, substituted or unsubstituted dialkyl- and diaryl-
5 aminoalkoxy groups, substituted or unsubstituted alkylarylaminoalkoxy groups. Particular examples include: -OCH₃, N-morpholinyl, -N-cis-dialkylmorpholinyl, -N-(4-alkyl)piperazinyl, or -OCH₂(2-pyridyl).

In yet preferred compounds having structure II, R⁵, R⁶, R⁷, and R⁸ are hydrogen. In still other more preferred compounds of structure II, R⁶, R⁷ or
10 both R⁶ and R⁷ are alkyl groups having from one to four carbon atoms. In yet other preferred compounds of structure II, R⁶ or R⁷ is an -OR¹⁶ group and R¹⁶ is an alkyl, aryl, heterocycl-, or heterocyclalkyl group. In still further preferred compounds of structure II, R⁶ or R⁷ is a -OCH₂(CH₂)_q(heterocycl-) group and q is 0, 1, 2, 3, or 4. In more preferred compounds in which R⁶ or R⁷ is a
15 -OCH₂(CH₂)_q(heterocycl-) group, the heterocycl group of the -OCH₂(CH₂)_n(heterocycl-) group is a heterocycle selected from substituted or unsubstituted morpholine, substituted or unsubstituted piperazine, substituted or unsubstituted piperidine, substituted or unsubstituted pyrrolidine, substituted or unsubstituted pyrrole, substituted or unsubstituted imidazole, substituted or
20 unsubstituted pyrazole, substituted or unsubstituted 1,2,3-triazole, substituted or unsubstituted 1,2,4-triazole, substituted or unsubstituted tetrazole, substituted or unsubstituted thiomorpholine, substituted or unsubstituted homopiperazine, substituted or unsubstituted oxazolidin-2-one, substituted or unsubstituted pyrrolidin-2-one, substituted or unsubstituted pyridine, substituted or unsubstituted
25 oxazole, substituted or unsubstituted isoxazole, substituted or unsubstituted thiazole, substituted or unsubstituted isothiazole, substituted or unsubstituted furan, substituted or unsubstituted thiophene, substituted or unsubstituted tetrahydrofuran, substituted or unsubstituted tetrahydrothiophene, substituted or unsubstituted benzimidazole, substituted or unsubstituted benzoxazole, or substituted or
30 unsubstituted benzothiazole.

WO 02/18383

PCT/US01/41942

-52-

- In compounds of structure II, R^9 and R^{15} may be the same or different and are selected from H, -OH, substituted or unsubstituted alkoxy groups, substituted or unsubstituted aryloxy groups, -NH₂, substituted or unsubstituted alkylamino groups, substituted or unsubstituted arylamino groups, substituted or unsubstituted dialkylamino groups, substituted or unsubstituted diarylamino groups, substituted or unsubstituted (alkyl)(aryl)amino groups, substituted or unsubstituted alkyl groups, substituted or unsubstituted aryl groups, -C(=O)H, -C(=O)-alkyl groups, or -C(=O)-aryl groups. In preferred compounds of structure II, R^9 is hydrogen.
- 10 In compounds of structure II, R^{10} is selected from substituted or unsubstituted alkyl groups, substituted or unsubstituted aryl groups, substituted or unsubstituted heterocyclyl groups, substituted or unsubstituted heterocyclylalkyl groups, -C(=O)H, -C(=O)-alkyl groups, -C(=O)-aryl groups, -C(=O)O-alkyl groups, -C(=O)O-aryl groups, -C(=O)NH₂, -C(=O)NH(alkyl) groups, -C(=O)NH(aryl) groups, -C(=O)N(alkyl)₂ groups, -C(=O)N(aryl)₂ groups, -C(=O)N(alkyl)(aryl) groups, -NH₂, -NH(alkyl) groups, -NH(aryl) groups, -N(alkyl)₂ groups, -N(alkyl)(aryl) groups, -N(aryl)₂ groups, -C(=O)NH(heterocyclyl) groups, -C(=O)N(heterocyclyl)₂ groups, -C(=O)-N(alkyl)(heterocyclyl) groups, or -C(=O)N(aryl)(heterocyclyl) groups.
- 15 20 R^{11} and R^{20} may be the same or different in compounds of structure II and are independently selected from substituted or unsubstituted alkyl groups, or substituted or unsubstituted aryl groups.
- 25 In compounds of structure II, R^{12} is selected from H, substituted or unsubstituted alkyl groups, substituted or unsubstituted aryl groups, or substituted or unsubstituted heterocyclyl groups whereas R^{13} is selected from H, substituted or unsubstituted alkyl groups, substituted or unsubstituted aryl groups, substituted or unsubstituted heterocyclyl groups, -OH, alkoxy groups, aryloxy groups, -NH₂, substituted or unsubstituted heterocyclylalkyl groups, substituted or unsubstituted aminoalkyl groups, substituted or unsubstituted alkylaminoalkyl groups, substituted

WO 02/18383

PCT/US01/41942

-53-

or unsubstituted dialkylaminoalkyl groups, substituted or unsubstituted arylaminoalkyl groups, substituted or unsubstituted diarylaminoalkyl groups, substituted or unsubstituted (alkyl)(aryl)aminoalkyl groups, substituted or unsubstituted alkylamino groups, substituted or unsubstituted arylamino groups, substituted or unsubstituted dialkylamino groups, substituted or unsubstituted diarylamino groups, substituted or unsubstituted (alkyl)(aryl)amino groups, -C(=O)H, -C(=O)-alkyl groups, -C(=O)-aryl groups, -C(=O)O-alkyl groups, -C(=O)O-aryl groups, -C(=O)NH₂, -C(=O)NH(alkyl) groups, -C(=O)NH(aryl) groups, -C(=O)N(alkyl)₂ groups, -C(=O)N(aryl)₂ groups, -C(=O)N(alkyl)(aryl) groups, -C(=O)-heterocyclyl groups, -C(=O)-O-heterocyclyl groups, -C(=O)NH(heterocyclyl) groups, -C(=O)-N(heterocyclyl)₂ groups, -C(=O)-N(alkyl)(heterocyclyl) groups, -C(=O)-N(aryl)(heterocyclyl) groups, substituted or unsubstituted heterocyclylaminoalkyl groups, substituted or unsubstituted hydroxyalkyl groups, substituted or unsubstituted alkoxyalkyl groups, substituted or unsubstituted aryloxyalkyl groups, or substituted or unsubstituted heterocycloxyalkyl groups. R¹² and R¹³ may join together to form a 5 to 7 membered saturated or unsaturated, substituted or unsubstituted N-containing ring.

In compounds of structure II, R¹⁴ is selected from H, -OH, alkoxy groups, aryloxy groups, -NH₂, -NH(alkyl) groups, -NH(aryl) groups, -N(alkyl)₂ groups, -N(aryl)₂ groups, -N(alkyl)(aryl) groups, substituted or unsubstituted alkyl groups, substituted or unsubstituted aryl groups, -NH(heterocyclyl) groups, -N(heterocyclyl)₂ groups, -N(alkyl)(heterocyclyl) groups, or -N(aryl)(heterocyclyl) groups.

In compounds of structure II, R¹⁶ is selected from substituted or unsubstituted alkyl groups, substituted or unsubstituted aryl groups, substituted or unsubstituted heterocyclyl groups, substituted or unsubstituted heterocyclylalkyl groups, -C(=O)H, -C(=O)-alkyl groups, -C(=O)-aryl groups, -C(=O)-heterocyclyl groups, -C(=O)NH₂, -C(=O)NH(alkyl) groups, -C(=O)NH(aryl) groups, -C(=O)N(alkyl)₂ groups, -C(=O)N(aryl)₂ groups,

WO 02/18383

PCT/US01/41942

-54-

- C(=O)N(alkyl)(aryl) groups, -C(=O)NH-heterocyclyl groups,
-C(=O)N-(heterocyclyl)₂ groups, -C(=O)N(alkyl)(heterocyclyl) groups,
-C(=O)N(aryl)(heterocyclyl) groups, substituted or unsubstituted aminoalkyl
groups, substituted or unsubstituted alkylaminoalkyl groups, substituted or
5 unsubstituted dialkylaminoalkyl groups, substituted or unsubstituted arylaminoalkyl
groups, substituted or unsubstituted diarylaminoalkyl groups, substituted or
unsubstituted (alkyl)(aryl)aminoalkyl groups, substituted or unsubstituted
heterocyclylaminoalkyl groups, substituted or unsubstituted
diheterocyclylaminoalkyl groups, substituted or unsubstituted
10 (heterocyclyl)(alkyl)aminoalkyl groups, substituted or unsubstituted
(heterocyclyl)(aryl)aminoalkyl groups, substituted or unsubstituted alkoxyalkyl
groups, substituted or unsubstituted aryloxyalkyl groups, substituted or
unsubstituted hydroxyalkyl groups, or substituted or unsubstituted
heterocycliloxyalkyl groups.
- 15 In compounds of structure II, R¹⁷ is selected from H, substituted or
unsubstituted alkyl groups, substituted or unsubstituted aryl groups, or substituted
or unsubstituted heterocyclyl groups whereas R¹⁸ is selected from H, substituted or
unsubstituted alkyl groups, substituted or unsubstituted aryl groups, substituted or
unsubstituted heterocyclyl groups, -C(=O)H, -C(=O)-alkyl groups, -C(=O)-aryl
20 groups, -C(=O)NH₂, -C(=O)NH(alkyl) groups, -C(=O)NH(aryl) groups,
-C(=O)N(alkyl)₂ groups, -C(=O)N(aryl)₂ groups, -C(=O)N(alkyl)(aryl) groups,
-C(=O)O-alkyl groups, -C(=O)O-aryl groups, substituted or unsubstituted
aminoalkyl groups, substituted or unsubstituted alkylaminoalkyl groups, substituted
or unsubstituted dialkylaminoalkyl groups, substituted or unsubstituted
25 arylaminoalkyl groups, substituted or unsubstituted diarylaminoalkyl groups,
substituted or unsubstituted (aryl)(alkyl)aminoalkyl groups, substituted or
unsubstituted heterocyclylalkyl groups, -C(=O)-heterocyclyl groups,
-C(=O)-O-heterocyclyl groups, -C(=O)NH(heterocyclyl) groups,
-C(=O)-N(heterocyclyl)₂ groups, -C(=O)-N(alkyl)(heterocyclyl) groups,
30 -C(=O)-N(aryl)(heterocyclyl) groups, substituted or unsubstituted

WO 02/18383

PCT/US01/41942

-55-

heterocyclylaminoalkyl groups, substituted and unsubstituted
diheterocyclylaminoalkyl groups, substituted and unsubstituted
(heterocyclyl)(alkyl)aminoalkyl groups, substituted and unsubstituted
(heterocyclyl)(aryl)aminoalkyl groups, substituted or unsubstituted hydroxyalkyl
5 groups, substituted or unsubstituted alkoxyalkyl groups, substituted or unsubstituted
aryloxyalkyl groups, or substituted or unsubstituted heterocycloxyalkyl groups.
R¹⁷ and R¹⁸ may join together to form a 5 to 7 membered saturated or unsaturated,
substituted or unsubstituted N-containing ring.

Finally, in compounds of structure II, R¹⁹, R²¹, and R²² may be the
10 same or different and are independently selected from H, -NH₂, -NH(alkyl) groups,
-NH(aryl) groups, -N(alkyl)₂ groups, -N(aryl)₂ groups, -N(alkyl)(aryl) groups,
-NH(heterocyclyl) groups, -N(heterocyclyl)(alkyl) groups, -N(heterocyclyl)(aryl)
groups, -N(heterocyclyl)₂ groups, substituted or unsubstituted alkyl groups,
substituted or unsubstituted aryl groups, -OH, substituted or unsubstituted alkoxy
15 groups, substituted or unsubstituted heterocyclyl groups, substituted or unsubstituted
aryloxy groups, heterocycloxy groups, -NHOH, -N(alkyl)OH groups, -N(aryl)OH
groups, -N(alkyl)O-alkyl groups, -N(aryl)O-alkyl groups, -N(alkyl)O-aryl groups,
or -N(aryl)O-aryl groups.

Preferred compounds having the structure II include those in which
20 R¹⁹ is selected from substituted or unsubstituted alkyl groups, substituted or
unsubstituted aryl groups, -NH₂, -NH(alkyl) groups, -N(alkyl)₂ groups, -NH(aryl)
groups, -N(aryl)₂ groups, -N(alkyl)(aryl) groups, -NH(heterocyclyl) groups,
-N(heterocyclyl)(alkyl) groups, -N(heterocyclyl)(aryl) groups, -N(heterocyclyl)₂
groups, or N-containing heterocycles, and the N-containing heterocycles are bonded
25 to the carbonyl carbon of the -C(=O)-R¹⁹ group through either a nitrogen atom or a
carbon atom in the rings of the N-containing heterocycles. In still more preferred
compounds in which R¹⁹ is a N-containing heterocycle, the N-containing heterocycle
of the R¹⁹ group is selected from substituted or unsubstituted morpholine,
substituted or unsubstituted pyrrolidine, substituted or unsubstituted piperazine,

WO 02/18383

PCT/US01/41942

-56-

substituted or unsubstituted piperidine, substituted or unsubstituted pyrrole,
substituted or unsubstituted imidazole, substituted or unsubstituted pyrazole,
substituted or unsubstituted 1,2,3-triazole, substituted or unsubstituted 1,2,4-
triazole, substituted or unsubstituted tetrazole, substituted or unsubstituted
5 thiomorpholine, substituted or unsubstituted homopiperazine, substituted or
unsubstituted oxazolidin-2-one, substituted or unsubstituted pyrrolidin-2-one,
substituted or unsubstituted pyridine, substituted or unsubstituted oxazole,
substituted or unsubstituted isoxazole, substituted or unsubstituted thiazole,
substituted or unsubstituted isothiazole, substituted or unsubstituted benzimidazole,
10 substituted or unsubstituted benzoxazole, or substituted or unsubstituted
benzothiazole.

Other preferred compounds having structure II are provided in which
R¹⁶ or R¹⁸ is selected from substituted or unsubstituted aminoalkyl groups,
substituted or unsubstituted alkylaminoalkyl groups, substituted or unsubstituted
15 arylaminoalkyl groups, substituted or unsubstituted dialkylaminoalkyl groups,
substituted or unsubstituted diarylaminoalkyl groups, alkylaryl aminoalkyl groups,
or substituted or unsubstituted heterocyclylalkyl groups, including: -CH₂(CH₂)_pNH₂
groups, -CH₂(CH₂)_pNH(alkyl) groups, -CH₂(CH₂)_pNH(aryl) groups,
-CH₂(CH₂)_pN(alkyl)₂ groups, -CH₂(CH₂)_pN(aryl)₂ groups, -CH₂(CH₂)_pN(alkyl)(aryl)
20 groups, or -CH₂(CH₂)_p(heterocyclyl) groups, where p is an integer ranging from 0
to 4 and the heterocyclyl group of the -CH₂(CH₂)_p(heterocyclyl) group is a N-
containing heterocycle selected from substituted or unsubstituted morpholine,
substituted or unsubstituted pyrrolidine, substituted or unsubstituted piperazine,
substituted or unsubstituted piperidine, substituted or unsubstituted pyrrole,
25 substituted or unsubstituted imidazole, substituted or unsubstituted pyrazole,
substituted or unsubstituted 1,2,3-triazole, substituted or unsubstituted 1,2,4-
triazole, substituted or unsubstituted tetrazole, substituted or unsubstituted
thiomorpholine, substituted or unsubstituted homopiperazine, substituted or
unsubstituted oxazolidin-2-one, substituted or unsubstituted pyrrolidin-2-one,
30 substituted or unsubstituted pyridine, substituted or unsubstituted oxazole,

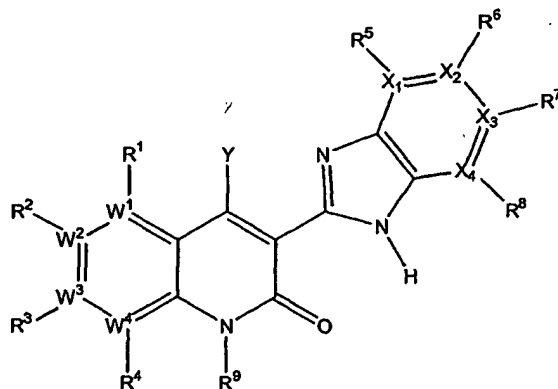
WO 02/18383

PCT/US01/41942

-57-

substituted or unsubstituted isoxazole, substituted or unsubstituted thiazole, substituted or unsubstituted isothiazole, substituted or unsubstituted benzimidazole, substituted or unsubstituted benzoxazole, or substituted or unsubstituted benzothiazole.

- 5 Other particularly preferred inhibitors of VEGF-RTK are compounds having the structure III, tautomers of the compounds, pharmaceutically acceptable salts of the compounds, and pharmaceutically acceptable salts of the tautomers. Structure III has the following formula:



III

- 10 In compounds of structure III, W¹, W², W³, and W⁴ are selected from C or N, and at least one of W¹, W², W³, or W⁴ is N. In some preferred compounds of structure III, W¹ is N and R¹ is absent or H. In other preferred compounds of structure III, W² is N and R² is absent or H. In still other preferred compounds of structure III, W³ is N and R³ is absent or H. In yet other preferred compounds of structure III, W⁴ is N and R⁴ is absent or H. In other preferred compounds of structure III, one of W¹, W², W³, and W⁴ is N whereas in other compounds of structure III, two of W¹, W², W³, and W⁴ are N. In yet other preferred embodiments, W¹, W², and W³ are all C and W⁴ is N; W¹, W², and W⁴ are all C and W³ is N; W¹, W³, and W⁴ are all C and W² is N; or W², W³, and W⁴ are all C and W¹ is N.
- 15
- 20

WO 02/18383

PCT/US01/41942

-58-

In compounds of structure III, X^1 , X^2 , X^3 , and X^4 are selected from C or N, and at least one of X^1 , X^2 , X^3 , or X^4 is N. In some preferred compounds of structure III, X^1 is N and R^5 is absent or H. In other preferred compounds of structure III, X^2 is N and R^6 is absent or H. In still other preferred compounds of structure III, X^3 is N and R^7 is absent or H. In yet other preferred compounds of structure III, X^4 is N and R^8 is absent or H. In other preferred compounds of structure III, one of X^1 , X^2 , X^3 , and X^4 is N whereas in other compounds of structure III, two of X^1 , X^2 , X^3 , and X^4 are N.

In compounds having structure III, Y is selected from H, -OH, -OR¹⁰ groups, -SH, -SR¹¹ groups, -NR¹²R¹³ groups, -CN, -C(=O)-R¹⁴ groups, substituted or unsubstituted alkyl groups, substituted or unsubstituted alkenyl groups, substituted or unsubstituted alkynyl groups, substituted or unsubstituted aralkyl groups, substituted or unsubstituted heterocyclalkyl groups, substituted or unsubstituted alkylaminoalkyl groups, substituted or unsubstituted dialkylaminoalkyl groups, substituted or unsubstituted arylaminoalkyl groups, substituted or unsubstituted diarylaminoalkyl groups, substituted or unsubstituted (alkyl)(aryl)aminoalkyl groups, substituted or unsubstituted heterocyclaminoalkyl groups, substituted and unsubstituted diheterocyclaminoalkyl groups, substituted and unsubstituted (heterocycl)(alkyl)aminoalkyl groups, substituted and unsubstituted (heterocycl)(aryl)aminoalkyl groups, substituted or unsubstituted heterocycl groups, substituted or unsubstituted aryl groups, substituted or unsubstituted hydroxyalkyl groups, substituted or unsubstituted alkoxyalkyl groups, substituted or unsubstituted aryloxyalkyl groups, or substituted or unsubstituted heterocycloxyalkyl groups.

In preferred compounds of structure III, Y is selected from H, -OH, -OR¹⁰ groups, or -NR¹²R¹³ groups. More preferably, Y is a -NR¹²R¹³ group. Still more preferably, Y is a -NR¹²R¹³ group and both R¹² and R¹³ are hydrogen. In other preferred compounds having the structure III, Y is selected from -N(CH₃)₂, -NH(CH₃), -NH(CH₂CH₃), -N(CH₂CH₃)₂, -NH(aryl) groups, -N(aryl)₂ groups,

WO 02/18383

PCT/US01/41942

-59-

- NHNH₂, -NHN(CH₃)₂, -N(CH₃)NH(CH₃), -NH(CH₂)_mNH₂ groups,
 -NH(CH₂)_mNH(alkyl) groups, -NH(CH₂)_mN(alkyl)₂ groups, -N(alkyl)(CH₂)_mNH₂
 groups, -N(alkyl)(CH₂)_mNH(alkyl) groups, -N(alkyl)(CH₂)_mN(alkyl)₂ groups,
 -NH(CH₂)_n(heterocyclyl) groups, -N(alkyl)[(CH₂)_n(heterocyclyl)] groups,
 5 -NH(CH₂)_mOH groups, -NH(CH₂)_mOCH₃ groups, -NHCH₂CH(NH₂)CH(CH₃)₂,
 -NH(2-aminocyclohexyl), -NH(cyclohexyl), -NHCH₃, -NH(N-morpholinyl),
 -NH(quinuclidyl), especially -NH(quinuclid-3-yl), and groups where R¹² and R¹³
 join to form a substituted or unsubstituted saturated 5 or 6 membered N-containing
 ring, where m is 2, 3, or 4 and n is 0, 1, 2, or 3. Still more preferred compounds
 10 of this type are those in which Y is selected from -NH(5-benzimidazolyl),
 -NH(CH₂)₂N(CH₃)₂, -NH(CH₂)₂OH, -NH(CH₂)(4-imidazolyl), -NH(CH₂)(3-
 imidazolyl), -NH(CH₂)(4-pyridyl), -NH(CH₂)(2-pyridyl), -NH(CH₂)(3-pyridyl),
 -NH(CH₂)(2-tetrahydrofuranyl), -NH(CH₂)(4-piperidinyl), -NH(CH₂)(3-
 piperidinyl), -NH(CH₂)₂[2-(N-methyl-pyrrolidinyl)], -NH(CH₂)₂(2-pyrrolidinyl),
 15 -NH(CH₂)[2-(N-methylpyrrolidinyl)], -NH(CH₂)(2-pyrrolidinyl), -NH(3-
 piperidinyl), or -NH(3-pyrrolidinyl).

- In compounds of structure III, R¹, R², R³, R⁴, R⁵, R⁶, R⁷, and R⁸ may
 be the same or different and are independently selected from H, Cl, Br, F, I, -NO₂,
 -CN, -OH, -OR¹⁵ groups, -NR¹⁶R¹⁷ groups, -C(=O)R¹⁸ groups, -SH, -SR¹⁹ groups,
 20 -S(=O)R²⁰ groups, S(=O)₂R²¹ groups, substituted or unsubstituted amidinyl groups,
 substituted or unsubstituted guanidinyl groups, substituted or unsubstituted primary,
 secondary, or tertiary alkyl groups, substituted or unsubstituted aryl groups,
 substituted or unsubstituted alkenyl groups, substituted or unsubstituted alkynyl
 groups, substituted or unsubstituted heterocyclyl groups, substituted or unsubstituted
 25 alkylaminoalkyl groups, substituted or unsubstituted dialkylaminoalkyl groups,
 substituted or unsubstituted arylaminoalkyl groups, substituted or unsubstituted
 diarylaminoalkyl groups, substituted or unsubstituted (alkyl)(aryl)aminoalkyl
 groups, substituted or unsubstituted heterocyclylalkyl groups, substituted or
 unsubstituted aminoalkyl groups, substituted or unsubstituted
 30 heterocyclylaminoalkyl groups, substituted and unsubstituted

WO 02/18383

PCT/US01/41942

-60-

diheterocyclylaminoalkyl groups, substituted and unsubstituted
(alkyl)(heterocyclyl)aminoalkyl groups, substituted and unsubstituted
(aryl)(heterocyclyl)aminoalkyl groups, substituted or unsubstituted hydroxyalkyl
groups, substituted or unsubstituted alkoxyalkyl groups, substituted or unsubstituted
5 aryloxyalkyl groups, or substituted or unsubstituted heterocyclyloxyalkyl groups,
and R¹ is absent or H if W¹ is N, R² is absent or H if W² is N, R³ is absent or H if
W³ is N, R⁴ is absent or H if W⁴ is N, R⁵ is absent or H if X¹ is N, R⁶ is absent or
H if X² is N, R⁷ is absent or H if X³ is N, and R⁸ is absent or H if X⁴ is N.

Some preferred compounds have the structure III where at least one
10 of R¹, R², R³, R⁴, R⁵, R⁶, R⁷, or R⁸ is a substituted or unsubstituted heterocyclyl
group selected from a group of heterocycles that includes morpholine, piperazine,
piperidine, 1,2,3-triazole, 1,2,4-triazole, tetrazole, pyrrolidine, pyrazole, pyrrole,
thiomorpholine, homopiperazine, benzimidazole, oxazolidin-2-one, pyrrolidin-2-
one, imidazole, isothiazole, thiazole, thiophene, furan, pyran, tetrahydrothiophene,
15 tetrahydrofuran, tetrahydropyran, and pyridine.

Still other preferred compounds having structure III are those in
which R¹, R², and R³ are H, and W⁴ is N. Still other compounds having the
formula of structure III are provided in which R², R³, and R⁴ are H, and W¹ is N.
Still other compounds having the formula of structure III are provided in which R¹,
20 R³, and R⁴ are H, and W² is N. Still other compounds having the formula of
structure III are provided in which R¹, R², and R⁴ are H, and W³ is N.

In other preferred compounds, R¹ or R² is selected from F, Cl,
substituted or unsubstituted alkoxy groups, substituted or unsubstituted
heterocyclyloxy groups, substituted or unsubstituted heterocyclylalkoxy groups,
25 substituted or unsubstituted heterocyclyl groups, substituted or unsubstituted alkyl-,
heterocyclyl-, or aryl-aminoalkyl groups, substituted or unsubstituted dialkyl- or
diaryl-aminoalkyl groups, substituted or unsubstituted alkylaryl-aminoalkyl groups,
substituted or unsubstituted alkyl- and aryl-aminoalkoxy groups, substituted or
unsubstituted dialkyl- and diaryl-aminoalkoxy groups, or substituted or

WO 02/18383

PCT/US01/41942

-61-

unsubstituted alkylarylaminooalkoxy groups. Particular examples include:
-C(=O)N(alkyl)₂ groups, -OCH₂CH₂(N-morpholinyl), N-morpholinyl,
-OCH₂CH₂N(alkyl)₂ groups, -OCH₂CH₂NH(alkyl) groups, -OCH₂CH₂NH₂,
-OCH₂CH₂NH(aryl) groups, -OCH₂CH₂N(aryl)₂ groups, alkoxy groups,
5 -OCH₂CH₂N(alkyl)(aryl) groups, -O(4-piperidinyl), -O[4-(1-alkyl)piperidinyl]
groups, -OCH₂(2-pyridyl), -O(3-pyrrolidinyl), or -O[3-(1-alkyl)pyrrolidinyl]
groups.

Still other preferred compounds include those in which R² is selected
from F, Cl, -NO₂, substituted or unsubstituted alkoxy groups, substituted or
10 unsubstituted heterocyclylalkoxy groups, substituted or unsubstituted heterocyclyl
groups, substituted or unsubstituted alkyl-, heterocycl-, or aryl-aminoalkyl groups,
substituted or unsubstituted dialkyl- and diaryl-aminoalkyl groups, substituted or
unsubstituted alkylarylaminooalkyl groups, substituted or unsubstituted alkyl- and
aryl-aminoalkoxy groups, substituted or unsubstituted dialkyl- and diaryl-
15 aminoalkoxy groups, substituted or unsubstituted alkylarylaminooalkoxy groups.
Particular examples include: -OCH₃, N-morpholinyl, -N-cis-dialkylmorpholinyl,
-N-(4-alkyl)piperazinyl, or -OCH₂(2-pyridyl).

In yet preferred compounds having structure III, R⁵, R⁶, and R⁷ are
hydrogen; and X⁴ is N. In still other more preferred compounds of structure III,
20 R⁶, R⁷ or both R⁶ and R⁷ are alkyl groups having from one to four carbon atoms. In
yet other preferred compounds of structure III, R⁶ or R⁷ is an -OR¹⁵ group and R¹⁵
is an alkyl, aryl, heterocyclyl, or heterocyclylalkyl group. In still further preferred
compounds of structure III, R⁶ or R⁷ is a -OCH₂(CH₂)_q(heterocyclyl) group and q is
0, 1, 2, 3, or 4. In more preferred compounds in which R⁶ or R⁷ is a
25 -OCH₂(CH₂)_q(heterocyclyl) group, the heterocyclyl group of the
-OCH₂(CH₂)_n(heterocyclyl) group is a heterocycle selected from substituted or
unsubstituted morpholine, substituted or unsubstituted piperazine, substituted or
unsubstituted piperidine, substituted or unsubstituted pyrrolidine, substituted or
unsubstituted pyrrole, substituted or unsubstituted imidazole, substituted or

WO 02/18383

PCT/US01/41942

-62-

- unsubstituted pyrazole, substituted or unsubstituted 1,2,3-triazole, substituted or unsubstituted 1,2,4-triazole, substituted or unsubstituted tetrazole, substituted or unsubstituted thiomorpholine, substituted or unsubstituted homopiperazine, substituted or unsubstituted oxazolidin-2-one, substituted or unsubstituted
- 5 pyrrolidin-2-one, substituted or unsubstituted pyridine, substituted or unsubstituted oxazole, substituted or unsubstituted isoxazole, substituted or unsubstituted thiazole, substituted or unsubstituted isothiazole, substituted or unsubstituted furan, substituted or unsubstituted thiophene, substituted or unsubstituted tetrahydrofuran, substituted or unsubstituted tetrahydrothiophene, substituted or unsubstituted
- 10 benzimidazole, substituted or unsubstituted benzoxazole, or substituted or unsubstituted benzothiazole.

- In compounds of structure III, R^9 is selected from H, -OH, substituted or unsubstituted alkoxy groups, substituted or unsubstituted aryloxy groups, -NH₂, substituted or unsubstituted alkylamino groups, substituted or
- 15 unsubstituted arylamino groups, substituted or unsubstituted dialkylamino groups, substituted or unsubstituted diarylamino groups, substituted or unsubstituted (alkyl)(aryl)amino groups, substituted or unsubstituted alkyl groups, substituted or unsubstituted aryl groups, -C(=O)H, -C(=O)-alkyl groups, or -C(=O)-aryl groups. One group of particularly preferred compounds of structure III are those in
- 20 which R^9 is hydrogen.

- In compounds of structure III, R^{10} is selected from substituted or unsubstituted alkyl groups, substituted or unsubstituted aryl groups, substituted or unsubstituted heterocyclyl groups, substituted or unsubstituted heterocyclylalkyl groups, -C(=O)H, -C(=O)-alkyl groups, -C(=O)-aryl groups, -C(=O)O-alkyl
- 25 groups, -C(=O)O-aryl groups, -C(=O)NH₂, -C(=O)NH(alkyl) groups, -C(=O)NH(aryl) groups, -C(=O)N(alkyl)₂ groups, -C(=O)N(aryl)₂ groups, -C(=O)N(alkyl)(aryl) groups, -NH₂, -NH(alkyl) groups, -NH(aryl) groups, -N(alkyl)₂ groups, -N(alkyl)(aryl) groups, -N(aryl)₂ groups,

WO 02/18383

PCT/US01/41942

-63-

-C(=O)NH(heterocyclyl) groups, -C(=O)N(heterocyclyl)₂ groups,
-C(=O)N(alkyl)(heterocyclyl) groups, or -C(=O)N(aryl)(heterocyclyl) groups;

In compounds of structure III, R¹¹ and R¹⁹ may be the same or different and are independently selected from substituted or unsubstituted alkyl groups, or substituted or unsubstituted aryl groups whereas R¹² is selected from H,
5 substituted or unsubstituted alkyl groups, substituted or unsubstituted aryl groups, or substituted or unsubstituted heterocyclyl groups.

In compounds of structure III, R¹³ is selected from H, substituted or unsubstituted alkyl groups, substituted or unsubstituted aryl groups, substituted or unsubstituted heterocyclyl groups, -OH, alkoxy groups, aryloxy groups, -NH₂,
10 substituted or unsubstituted heterocyclylalkyl groups, substituted or unsubstituted aminoalkyl groups, substituted or unsubstituted alkylaminoalkyl groups, substituted or unsubstituted dialkylaminoalkyl groups, substituted or unsubstituted arylaminoalkyl groups, substituted or unsubstituted diarylaminoalkyl groups,
15 substituted or unsubstituted (alkyl)(aryl)aminoalkyl groups, substituted or unsubstituted alkylamino groups, substituted or unsubstituted arylamino groups, substituted or unsubstituted dialkylamino groups, substituted or unsubstituted diarylamino groups, substituted or unsubstituted (alkyl)(aryl)amino groups,
-C(=O)H, -C(=O)-alkyl groups, -C(=O)-aryl groups, -C(=O)O-alkyl groups,
20 -C(=O)O-aryl groups, -C(=O)NH₂, -C(=O)NH(alkyl) groups, -C(=O)NH(aryl) groups, -C(=O)N(alkyl)₂ groups, -C(=O)N(aryl)₂ groups, -C(=O)N(alkyl)(aryl) groups, -C(=O)-heterocyclyl groups, -C(=O)-O-heterocyclyl groups,
-C(=O)NH(heterocyclyl) groups, -C(=O)-N(heterocyclyl)₂ groups,
-C(=O)-N(alkyl)(heterocyclyl) groups, -C(=O)-N(aryl)(heterocyclyl) groups,
25 substituted or unsubstituted heterocyclylaminoalkyl groups, substituted or unsubstituted hydroxyalkyl groups, substituted or unsubstituted alkoxyalkyl groups, substituted or unsubstituted aryloxyalkyl groups, or substituted or unsubstituted heterocycliloxyalkyl groups. R¹² and R¹³ may join together to form a 5 to 7 membered saturated or unsaturated, substituted or unsubstituted N-containing ring.

WO 02/18383

PCT/US01/41942

-64-

In compounds of structure III, R¹⁴ is selected from H, -OH, alkoxy groups, aryloxy groups, -NH₂, -NH(alkyl) groups, -NH(aryl) groups, -N(alkyl)₂ groups, -N(aryl)₂ groups, -N(alkyl)(aryl) groups, substituted or unsubstituted alkyl groups, substituted or unsubstituted aryl groups, -NH(heterocyclyl) groups, 5 -N(heterocyclyl)₂ groups, -N(alkyl)(heterocyclyl) groups, or -N(aryl)(heterocyclyl) groups.

In compounds of structure III, R¹⁵ is selected from substituted or unsubstituted alkyl groups, substituted or unsubstituted aryl groups, substituted or unsubstituted heterocyclyl groups, substituted or unsubstituted heterocyclylalkyl 10 groups, -C(=O)H, -C(=O)-alkyl groups, -C(=O)-aryl groups, -C(=O)-heterocyclyl groups, -C(=O)NH₂, -C(=O)NH(alkyl) groups, -C(=O)NH(aryl) groups, -C(=O)N(alkyl)₂ groups, -C(=O)N(aryl)₂ groups, -C(=O)N(alkyl)(aryl) groups, -C(=O)NH-heterocyclyl groups, -C(=O)N-(heterocyclyl)₂ groups, -C(=O)N(alkyl)(heterocyclyl) groups, 15 -C(=O)N(aryl)(heterocyclyl) groups, substituted or unsubstituted aminoalkyl groups, substituted or unsubstituted alkylaminoalkyl groups, substituted or unsubstituted dialkylaminoalkyl groups, substituted or unsubstituted arylaminoalkyl groups, substituted or unsubstituted diarylaminoalkyl groups, substituted or unsubstituted (alkyl)(aryl)aminoalkyl groups, substituted or unsubstituted 20 heterocyclylaminoalkyl groups, substituted or unsubstituted diheterocyclylaminoalkyl groups, substituted or unsubstituted (heterocyclyl)(alkyl)aminoalkyl groups, substituted or unsubstituted (heterocyclyl)(aryl)aminoalkyl groups, substituted or unsubstituted alkoxyalkyl groups, substituted or unsubstituted aryloxyalkyl groups, substituted or 25 unsubstituted hydroxyalkyl groups, or substituted or unsubstituted heterocyclyloxyalkyl groups.

In compounds of structure III, R¹⁶ is selected from H, substituted or unsubstituted alkyl groups, substituted or unsubstituted aryl groups, or substituted or unsubstituted heterocyclyl groups whereas R¹⁷ is selected from H, substituted or

WO 02/18383

PCT/US01/41942

-65-

- unsubstituted alkyl groups, substituted or unsubstituted aryl groups, substituted or unsubstituted heterocyclyl groups, -C(=O)H, -C(=O)-alkyl groups, -C(=O)-aryl groups, -C(=O)NH₂, -C(=O)NH(alkyl) groups, -C(=O)NH(aryl) groups, -C(=O)N(alkyl)₂ groups, -C(=O)N(aryl)₂ groups, -C(=O)N(alkyl)(aryl) groups,
- 5 -C(=O)O-alkyl groups, -C(=O)O-aryl groups, substituted or unsubstituted aminoalkyl groups, substituted or unsubstituted alkylaminoalkyl groups, substituted or unsubstituted dialkylaminoalkyl groups, substituted or unsubstituted arylaminoalkyl groups, substituted or unsubstituted diarylaminoalkyl groups, substituted or unsubstituted (aryl)(alkyl)aminoalkyl groups, substituted or
- 10 unsubstituted heterocyclylalkyl groups, -C(=O)-heterocyclyl groups, -C(=O)-O-heterocyclyl groups, -C(=O)NH(heterocyclyl) groups, -C(=O)-N(heterocyclyl)₂ groups, -C(=O)-N(alkyl)(heterocyclyl) groups, -C(=O)-N(aryl)(heterocyclyl) groups, substituted or unsubstituted heterocyclylaminoalkyl groups, substituted and unsubstituted
- 15 diheterocyclylaminoalkyl groups, substituted and unsubstituted (heterocyclyl)(alkyl)aminoalkyl groups, substituted and unsubstituted (heterocyclyl)(aryl)aminoalkyl groups, substituted or unsubstituted hydroxyalkyl groups, substituted or unsubstituted alkoxyalkyl groups, substituted or unsubstituted aryloxyalkyl groups, or substituted or unsubstituted heterocycloxyalkyl groups.
- 20 R¹⁶ and R¹⁷ may join together to form a 5 to 7 membered saturated or unsaturated, substituted or unsubstituted N-containing ring.

Finally, in compounds of structure III, R¹⁸, R²⁰, and R²¹ may be the same or different and are independently selected H, -NH₂, -NH(alkyl) groups, -NH(aryl) groups, -N(alkyl)₂ groups, -N(aryl)₂ groups, -N(alkyl)(aryl) groups,

25 -NH(heterocyclyl) groups, -N(heterocyclyl)(alkyl) groups, -N(heterocyclyl)(aryl) groups, -N(heterocyclyl)₂ groups, substituted or unsubstituted alkyl groups, substituted or unsubstituted aryl groups, -OH, substituted or unsubstituted alkoxy groups, substituted or unsubstituted heterocyclyl groups, substituted or unsubstituted aryloxy groups, heterocycloxy groups, -NHOH, -N(alkyl)OH groups, -N(aryl)OH

WO 02/18383

PCT/US01/41942

-66-

groups, -N(alkyl)O-alkyl groups, -N(aryl)O-alkyl groups, -N(alkyl)O-aryl groups, or -N(aryl)O-aryl groups.

Preferred compounds having the structure III include those in which R¹⁸ is selected from substituted or unsubstituted alkyl groups, substituted or unsubstituted aryl groups, -NH₂, -NH(alkyl) groups, -N(alkyl)₂ groups, -NH(aryl) groups, -N(aryl)₂ groups, -N(alkyl)(aryl) groups, -NH(heterocyclyl) groups, -N(heterocyclyl)(alkyl) groups, -N(heterocyclyl)(aryl) groups, -N(heterocyclyl)₂ groups, or N-containing heterocycles, and the N-containing heterocycles are bonded to the carbonyl carbon of the -C(=O)-R¹⁸ group through either a nitrogen atom or a carbon atom in the rings of the N-containing heterocycles. In still more preferred compounds in which R¹⁸ is a N-containing heterocycle, the N-containing heterocycle of the R¹⁸ group is selected from substituted or unsubstituted morpholine, substituted or unsubstituted pyrrolidine, substituted or unsubstituted piperazine, substituted or unsubstituted piperidine, substituted or unsubstituted pyrrole, substituted or unsubstituted imidazole, substituted or unsubstituted pyrazole, substituted or unsubstituted 1,2,3-triazole, substituted or unsubstituted 1,2,4-triazole, substituted or unsubstituted tetrazole, substituted or unsubstituted thiomorpholine, substituted or unsubstituted homopiperazine, substituted or unsubstituted oxazolidin-2-one, substituted or unsubstituted pyrrolidin-2-one, substituted or unsubstituted pyridine, substituted or unsubstituted oxazole, substituted or unsubstituted isoxazole, substituted or unsubstituted thiazole, substituted or unsubstituted isothiazole, substituted or unsubstituted benzimidazole, substituted or unsubstituted benzoxazole, or substituted or unsubstituted benzothiazole.

Other preferred compounds having structure III are provided in which R¹⁵ or R¹⁷ is selected from substituted or unsubstituted aminoalkyl groups, substituted or unsubstituted alkylaminoalkyl groups, substituted or unsubstituted arylaminoalkyl groups, substituted or unsubstituted dialkylaminoalkyl groups, substituted or unsubstituted diarylaminoalkyl groups, alkylaryl aminoalkyl groups,

WO 02/18383

PCT/US01/41942

-67-

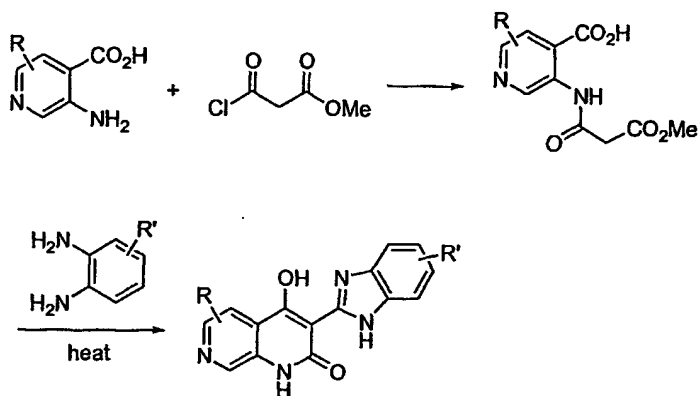
or substituted or unsubstituted heterocyclalkyl groups, including: $-\text{CH}_2(\text{CH}_2)_p\text{NH}_2$ groups, $-\text{CH}_2(\text{CH}_2)_p\text{NH}(\text{alkyl})$ groups, $-\text{CH}_2(\text{CH}_2)_p\text{NH}(\text{aryl})$ groups, $-\text{CH}_2(\text{CH}_2)_p\text{N}(\text{alkyl})_2$ groups, $-\text{CH}_2(\text{CH}_2)_p\text{N}(\text{aryl})_2$ groups, $-\text{CH}_2(\text{CH}_2)_p\text{N}(\text{alkyl})(\text{aryl})$ groups, or $-\text{CH}_2(\text{CH}_2)_p(\text{heterocycl})$ groups, where p is an integer ranging from 0 to 4 and the heterocycl group of the $-\text{CH}_2(\text{CH}_2)_p(\text{heterocycl})$ group is a N-containing heterocycle selected from substituted or unsubstituted morpholine, substituted or unsubstituted pyrrolidine, substituted or unsubstituted piperazine, substituted or unsubstituted piperidine, substituted or unsubstituted pyrrole, substituted or unsubstituted imidazole, substituted or unsubstituted pyrazole, substituted or unsubstituted 1,2,3-triazole, substituted or unsubstituted 1,2,4-triazole, substituted or unsubstituted tetrazole, substituted or unsubstituted thiomorpholine, substituted or unsubstituted homopiperazine, substituted or unsubstituted oxazolidin-2-one, substituted or unsubstituted pyrrolidin-2-one, substituted or unsubstituted pyridine, substituted or unsubstituted oxazole, substituted or unsubstituted isoxazole, substituted or unsubstituted thiazole, substituted or unsubstituted isothiazole, substituted or unsubstituted benzimidazole, substituted or unsubstituted benzoxazole, or substituted or unsubstituted benzothiazole.

Compounds of structure I and structure II may be synthesized from simple starting molecules as shown in Schemes 1-3 and exemplified in the Examples. As shown in Scheme 1, compounds of structure I and II may generally be prepared using pyridines or other heterocycles substituted with amines and carboxylic acid groups.

WO 02/18383

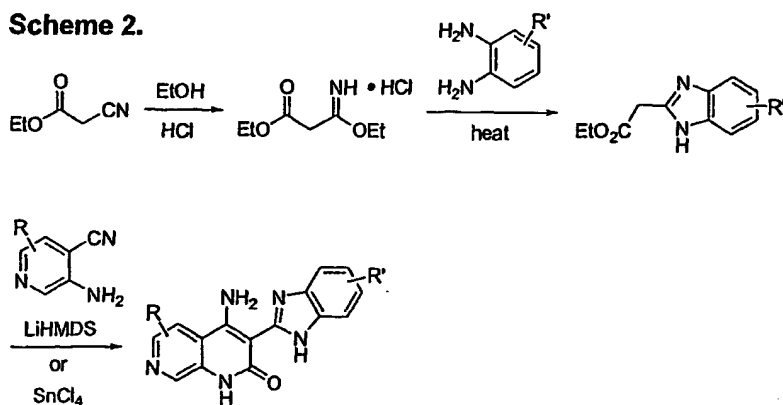
PCT/US01/41942

-68-

Scheme 1.

As shown in Scheme 1, a substituted pyridine such as a substituted or unsubstituted 3-amino-pyridine-4-carboxylic acid may be reacted with an acyl halide such as methyl 2-(chlorocarbonyl)acetate to produce an amide that will react with a substituted or unsubstituted 1,2-diaminobenzene. The resulting product is a 4-hydroxy-substituted compound of structure I or II. The use of starting pyridines with different substitution patterns such as 2-aminonicotinic acid (2-aminopyridine-4-carboxylic acid) provides compounds where the nitrogen is in a different position in the pyridine ring of the final compound. One skilled in the art will recognize that the procedure set forth in Scheme 1 may be modified to produce various compounds.

A method for preparing 4-amino substituted compounds of structures I and II is shown in Scheme 2.

Scheme 2.

WO 02/18383

PCT/US01/41942

-69-

As shown in Scheme 2, pyridines and other heterocycles substituted with amine and nitrile groups may be used to synthesize 4-amino substituted compounds of Structure I and II. A compound such as ethyl 2-cyanoacetate may be reacted with ethanol to produce ethyl 3-ethoxy-3-iminopropanoate hydrochloride.

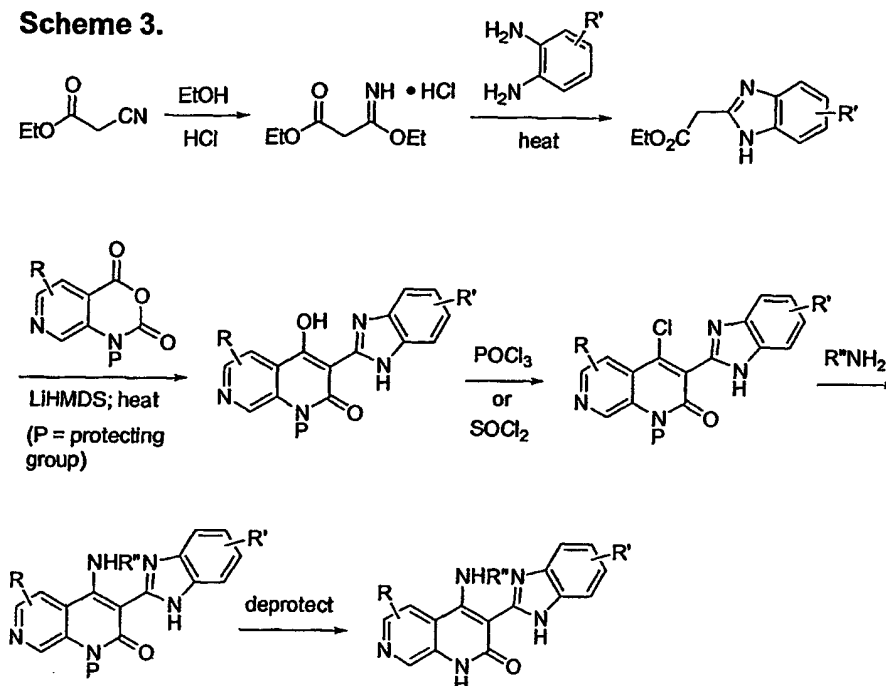
- 5 Subsequent reaction with a substituted or unsubstituted 1,2-phenylenediamine provides substituted or unsubstituted ethyl 2-benzimidazol-2-ylacetate. Reaction of a substituted or unsubstituted ethyl 3 benzimidazol-2-ylacetate with a pyridine having an amine and nitrile group such as substituted or unsubstituted 3-amino-4-cyanopyridine with a base such as lithium bis(trimethylsilyl)amide or a Lewis acid
10 such as tin tetrachloride provides the substituted or unsubstituted 4-amino substituted compound of structure I and II.

- Scheme 3 illustrates a general synthetic route that allows for the synthesis of 4-dialkylamino and 4-alkylamino compounds of structures I and II. An inspection of Scheme 3 shows that 4-hydroxy substituted compounds of structure I
15 or II may be converted into the 4-chloro derivative by reaction with phosphorous oxychloride. The 4-chloro derivative may then be reacted with an alkylamine or dialkylamine to produce the corresponding 4-alkylamino or 4-dialkylamino derivative. Deprotection affords the final 4-alkylamino or 4-dialkylamino compounds of structure I and II. Other groups that may be reacted with the 4-
20 chloro derivative in this manner include, but are not limited to, ROH, RSH, and CuCN.

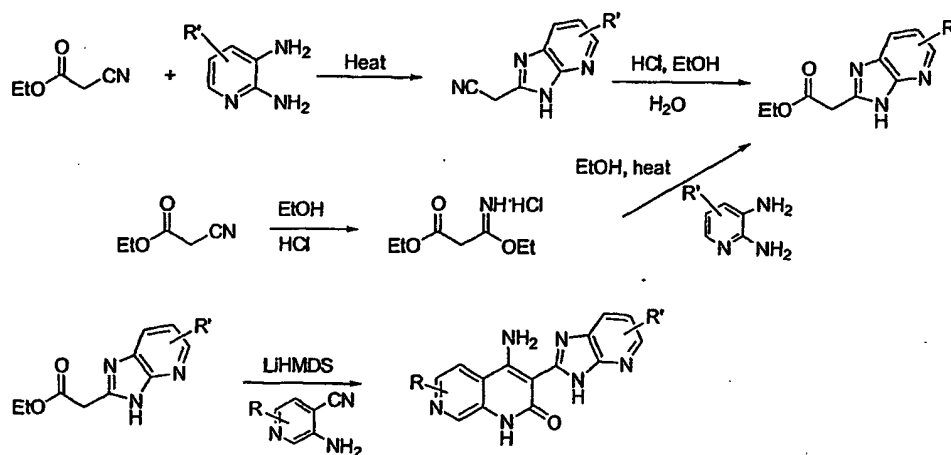
WO 02/18383

PCT/US01/41942

-70-

Scheme 3.

Heteroaromatic diamines may be used as precursors of compounds of structure III. The synthesis of compounds of structure III where $Y \equiv \text{NH}_2$ is depicted in Scheme 4.

Scheme 4.

5

A compound such as ethyl cyanoacetate may be condensed with a substituted or unsubstituted heterocycle containing two ortho amino groups such as

WO 02/18383

PCT/US01/41942

-71-

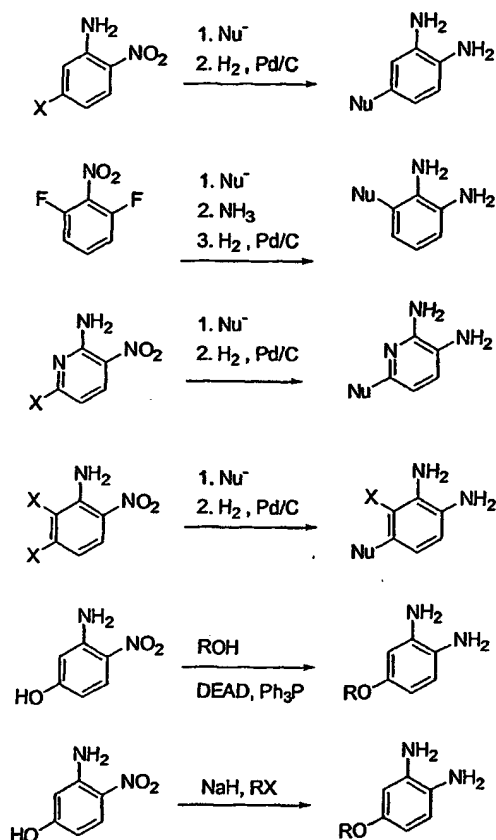
a substituted or unsubstituted 1,2-diaminopyridine to obtain a substituted or unsubstituted 2-imidazolo[5,4-b]pyridin-2-ylethanenitrile, which may be hydrolyzed in acidic medium to provide a substituted or unsubstituted ethyl 2-imidazolo[5,4-b]pyridin-2-ylacetate. As an alternate route, a substituted or unsubstituted ethyl 2-imidazolo[5,4-b]pyridin-2-ylacetate may be obtained from a compound such as the hydrochloride salt of 3-ethoxy-3-iminopropanoate and a substituted or unsubstituted 1,2-diaminopyridine. Reaction of a substituted or unsubstituted ethyl 2-imidazolo[5,4-b]pyridin-2-ylacetates with a pyridine having an amine and nitrile group such as a substituted or unsubstituted 3-amino-4-cyanopyridine and a base such as lithium bis(trimethylsilyl)amide provides the substituted or unsubstituted compound of structure III.

Scheme 5 illustrates just a few of the methods that may be used to produce a variety of 2-amino anilines. Halo (X = halogen) nitroanilines may be reacted with a wide variety of nucleophiles (Nu⁻) such as alcohols and amines to produce functionalized nitroanilines which may subsequently be reduced to diamines. The alcohol moiety of a nitroamino phenol may be modified using known methods to introduce a broad range of substituents into a diamine for subsequent inclusion in compound of the invention.

WO 02/18383

PCT/US01/41942

-72-

Scheme 5.

The instant invention also provides for compositions which may be prepared by mixing one or more compounds of the instant invention, or pharmaceutically acceptable salts or tautomers thereof, with pharmaceutically acceptable carriers, excipients, binders, diluents or the like to treat or ameliorate a variety of disorders related to the activity of VEGF-RTK, more particularly angiogenesis associated with cancer. Such compositions can be in the form of, for example, granules, powders, tablets, capsules, syrup, suppositories, injections, emulsions, elixirs, suspensions or solutions. The instant compositions can be formulated for various routes of administration, for example, by oral administration, by nasal administration, by rectal administration, subcutaneous injection, intravenous injection, intramuscular injections, or intraperitoneal injection. The following dosage

WO 02/18383

PCT/US01/41942

-73-

forms are given by way of example and should not be construed as limiting the instant invention.

For oral, buccal, and sublingual administration, powders, suspensions, granules, tablets, pills, capsules, gelcaps, and caplets are acceptable as solid dosage forms. These can be prepared, for example, by mixing one or more compounds of the instant invention, or pharmaceutically acceptable salts or tautomers thereof, with at least one additive such as a starch or other additive. Suitable additives are sucrose, lactose, cellulose sugar, mannitol, maltitol, dextran, starch, agar, alginates, chitins, chitosans, pectins, tragacanth gum, gum arabic, gelatins, collagens, casein, albumin, synthetic or semi-synthetic polymers or glycerides. Optionally, oral dosage forms can contain other ingredients to aid in administration, such as an inactive diluent, or lubricants such as magnesium stearate, or preservatives such as paraben or sorbic acid, or anti-oxidants such as ascorbic acid, tocopherol or cysteine, a disintegrating agent, binders, thickeners, buffers, sweeteners, flavoring agents or perfuming agents. Tablets and pills may be further treated with suitable coating materials known in the art.

Liquid dosage forms for oral administration may be in the form of pharmaceutically acceptable emulsions, syrups, elixirs, suspensions, and solutions, which may contain an inactive diluent, such as water. Pharmaceutical formulations may be prepared as liquid suspensions or solutions using a sterile liquid, such as, but not limited to, an oil, water, an alcohol, and combinations of these. Pharmaceutically suitable surfactants, suspending agents, emulsifying agents, may be added for oral or parenteral administration.

As noted above, suspensions may include oils. Such oil include, but are not limited to, peanut oil, sesame oil, cottonseed oil, corn oil and olive oil. Suspension preparation may also contain esters of fatty acids such as ethyl oleate, isopropyl myristate, fatty acid glycerides and acetylated fatty acid glycerides. Suspension formulations may include alcohols, such as, but not limited to, ethanol, isopropyl alcohol, hexadecyl alcohol, glycerol and propylene glycol. Ethers, such

WO 02/18383

PCT/US01/41942

-74-

as but not limited to, poly(ethyleneglycol), petroleum hydrocarbons such as mineral oil and petrolatum; and water may also be used in suspension formulations.

For nasal administration, the pharmaceutical formulations may be a spray or aerosol containing and appropriate solvents and optionally other
5 compounds such as, but not limited to, stabilizers, antimicrobial agents, antioxidants, pH modifiers, surfactants, bioavailability modifiers and combinations of these. A propellant for an aerosol formulation may include compressed air, nitrogen, carbon dioxide, or a hydrocarbon based low boiling solvent.

Injectable dosage forms generally include aqueous suspensions or oil
10 suspensions which may be prepared using a suitable dispersant or wetting agent and a suspending agent. Injectable forms may be in solution phase or in the form of a suspension, which is prepared with a solvent or diluent. Acceptable solvents or vehicles include sterilized water, Ringer's solution, or an isotonic aqueous saline solution. Alternatively, sterile oils may be employed as solvents or suspending
15 agents. Preferably, the oil or fatty acid is non-volatile, including natural or synthetic oils, fatty acids, mono-, di- or tri-glycerides.

For injection, the pharmaceutical formulation may be a powder suitable for reconstitution with an appropriate solution as described above. Examples of these include, but are not limited to, freeze dried, rotary dried or spray
20 dried powders, amorphous powders, granules, precipitates, or particulates. For injection, the formulations may optionally contain stabilizers, pH modifiers, surfactants, bioavailability modifiers and combinations of these.

For rectal administration, the pharmaceutical formulations may be in the form of a suppository, an ointment, an enema, a tablet or a cream for release of
25 compound in the intestines, sigmoid flexure and/or rectum. Rectal suppositories are prepared by mixing one or more compounds of the instant invention, or pharmaceutically acceptable salts or tautomers of the compound, with acceptable vehicles, for example, cocoa butter or polyethylene glycol, which is present in a solid

WO 02/18383

PCT/US01/41942

-75-

phase at normal storing temperatures, and present in a liquid phase at those temperatures suitable to release a drug inside the body, such as in the rectum. Oils may also be employed in the preparation of formulations of the soft gelatin type and suppositories. Water, saline, aqueous dextrose and related sugar solutions, and
5 glycerols may be employed in the preparation of suspension formulations which may also contain suspending agents such as pectins, carbomers, methyl cellulose, hydroxypropyl cellulose or carboxymethyl cellulose, as well as buffers and preservatives.

Besides those representative dosage forms described above,
10 pharmaceutically acceptable excipients and carries are generally known to those skilled in the art and are thus included in the instant invention. Such excipients and carriers are described, for example, in "Remingtons Pharmaceutical Sciences" Mack Pub. Co., New Jersey (1991), which is incorporated herein by reference.

The formulations of the invention may be designed for to be short-
15 acting, fast-releasing, long-acting, and sustained-releasing as described below. Thus, the pharmaceutical formulations may also be formulated for controlled release or for slow release.

The instant compositions may also comprise, for example, micelles or liposomes, or some other encapsulated form, or may be administered in an
20 extended release form to provide a prolonged storage and/or delivery effect. Therefore, the pharmaceutical formulations may be compressed into pellets or cylinders and implanted intramuscularly or subcutaneously as depot injections or as implants such as stents. Such implants may employ known inert materials such as silicones and biodegradable polymers.

25 Specific dosages may be adjusted depending on conditions of disease, the age, body weight, general health conditions, sex, and diet of the subject, dose intervals, administration routes, excretion rate, and combinations of drugs. Any of the above dosage forms containing effective amounts are well within the bounds of

WO 02/18383

PCT/US01/41942

-76-

routine experimentation and therefore, well within the scope of the instant invention.

A therapeutically effective dose may vary depending upon the route of administration and dosage form. The preferred compound or compounds of the instant invention is a formulation that exhibits a high therapeutic index. The therapeutic index is the dose ratio between toxic and therapeutic effects which can be expressed as the ratio between LD₅₀ and ED₅₀. The LD₅₀ is the dose lethal to 50% of the population and the ED₅₀ is the dose therapeutically effective in 50% of the population. The LD₅₀ and ED₅₀ are determined by standard pharmaceutical procedures in animal cell cultures or experimental animals.

"Treating" within the context of the instant invention, means an alleviation of symptoms associated with a disorder or disease, or halt of further progression or worsening of those symptoms, or prevention or prophylaxis of the disease or disorder. For example, within the context of treating patients in need of an inhibitor of VEGF-RTK, successful treatment may include a reduction in the proliferation of capillaries feeding a tumor or diseased tissue, an alleviation of symptoms related to a cancerous growth or tumor, proliferation of capillaries, or diseased tissue, a halting in capillary proliferation, or a halting in the progression of a disease such as cancer or in the growth of cancerous cells. Treatment may also include administering the pharmaceutical formulations of the present invention in combination with other therapies. For example, the compounds and pharmaceutical formulations of the present invention may be administered before, during, or after surgical procedure and/or radiation therapy. The compounds of the invention can also be administered in conjunction with other anti-cancer drugs including those used in antisense and gene therapy. Examples of standard chemotherapeutic agents that the compounds of the present may be used with include, but are not limited to, cisplatin, taxol, and 5-fluorouracil.

WO 02/18383

PCT/US01/41942

-77-

Pharmaceutical formulations according to the invention include any of the compounds described above in combination with a pharmaceutically acceptable carrier.

5 A method of treating a patient in need of an inhibitor of vascular endothelial growth factor receptor tyrosine kinase includes administering an effective amount of a pharmaceutical formulation according to the invention to a patient in need thereof.

10 A method for inhibiting tumor growth in a patient includes administering an effective amount of the compound or a pharmaceutically acceptable salt thereof to a patient having a tumor.

A method for inhibiting the proliferation of capillaries in a patient includes administering an effective amount of the compound or a pharmaceutically acceptable salt thereof according to a patient in need.

15 A method of preparing pharmaceutical formulations includes mixing any of the above-described compounds with a pharmaceutically acceptable carrier and water or an aqueous solution.

The present invention, thus generally described, will be understood more readily by reference to the following examples, which are provided by way of illustration and are not intended to be limiting of the present invention.

WO 02/18383

PCT/US01/41942

-78-

EXAMPLES

The following abbreviations are used throughout the Examples:

	ATP:	Adenosine triphosphate
	BSA:	Bovine Serum Albumin
5	DMSO:	Dimethylsulfoxide
	DTT:	DL-Dithiothreitol
	EDTA:	Ethylene diamine tetraacetic acid
	EtOAc:	Ethyl acetate
	EtOH:	Ethanol
10	HBTU:	O-Benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate
	IC ₅₀ value:	The concentration of an inhibitor that causes a 50 percent reduction in a measured activity
	LiHMDS:	Lithium bis(trimethylsilyl)amide
15	MeOH:	Methanol
	NaOH:	Sodium hydroxide
	NaOMe:	Sodium methoxide
	NMP:	N-methylpyrrolidone
	TFA:	Trifluoroacetic acid
20	THF:	Tetrahydrofuran

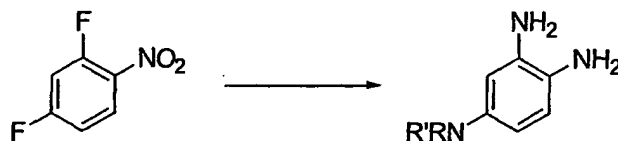
Various functionalized aryl diamines were obtained from commercial sources, prepared by methods known to those of skill in the art, or were prepared by the following general methods. The compounds were named using Nomenclator (v. 3.0 & v. 5.0) from ChemInnovation Software, Inc. and ACD/Name v. 4.53.

25 The various aryl diamine starting materials used to synthesize benzimidazole acetates may be obtained from commercial sources, prepared by methods known to one of skill in the art, or prepared by the following general methods 1-7.

WO 02/18383

PCT/US01/41942

-79-

Method 1

- 2,4-Difluoronitrobenzene (1.0 eq) was placed in a dry round-bottomed flask equipped with a dry ice condenser charged with acetone and dry ice.
- 5 Ammonia was condensed into the flask and the resulting solution was stirred at reflux for 7 hours. A yellow precipitate formed within 1 hour. After 7 hours, the condenser was removed and the liquid ammonia was allowed to evaporate over several hours. The crude product was purified by flash chromatography on silica gel (85:15 hexanes:ethyl acetate, product at $R_f = 0.32$, contaminant at $R_f = 0.51$);
- 10 GC/MS m/z 156.1 (M^+), R_t 11.16 minutes.

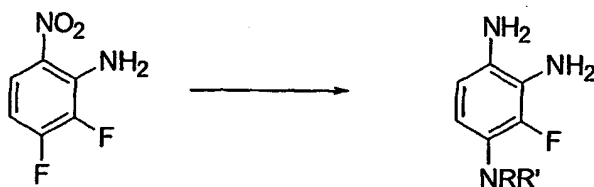
- The resulting 5-fluoro-2-nitrophenylamine (1.0 eq) and an amine (1.1 eq) e.g. N-methyl piperazine, were dissolved in NMP and triethylamine (2.0 eq) was added. The reaction mixture was heated at 100°C for 3 hours. The solution was then cooled to room temperature and diluted with water. The resulting
- 15 precipitate was filtered and dried under vacuum to provide the 2-nitro-diamino product. Alternatively, the same product may be obtained from commercially available 5-chloro-2-nitrophenylamine under identical conditions except heating at 130°C for 1-2 days. In some examples, the displacement on either 5-fluoro-2-nitrophenylamine or 5-chloro-2-nitrophenylamine can be conducted in neat amine (5
- 20 eq) at 100°C or 130 °C, respectively. The product is isolated in an identical manner. LC/MS m/z 237.1 (MH^+), R_t 1.304 minutes.

- The nitroamine (1.0 eq) and 10% Pd/C (0.1 eq) was suspended in anhydrous ethanol at room temperature. The reaction flask was evacuated and subsequently filled with H_2 . The resulting mixture was then stirred under a
- 25 hydrogen atmosphere overnight. The resulting solution was filtered through Celite and concentrated under vacuum to provide the crude product which was used without further purification.

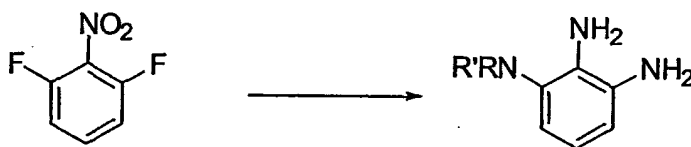
WO 02/18383

PCT/US01/41942

-80-

Method 2

A round-bottom flask was charged with 2,3-difluoro-6-nitrophenylamine (1 eq) and enough NMP to make a viscous slurry. An amine (5 eq), e.g. N-methyl piperazine, was added and the solution was heated at 100°C. After 2 hours, the solution was cooled and poured into water. A bright yellow solid formed which was filtered and dried. The nitroamine was reduced as in Method 1 to provide the crude product which was used without further purification. LC/MS *m/z* 225.1 (MH⁺), *R*_t 0.335 minutes.

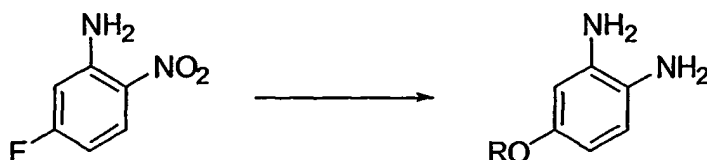
Method 3

To a 0.1 M DMF solution of 1,3-difluoro-2-nitrobenzene was added Et₃N (2 eq) followed by an amine (1 eq), e.g. morpholine. The mixture was stirred for 18 hours and then diluted with water and extracted with ethyl acetate. LC/MS *m/z* 227.2 (MH⁺), *R*_t 2.522 minutes. The combined organic layers were dried over MgSO₄, filtered, and concentrated. Ammonia was condensed into a bomb containing the crude product. The bomb was sealed and heated to 100°C (over 400 psi). After 72 hours the bomb was allowed to cool and the ammonia was evaporated to provide a reddish solid. The nitroamine was reduced as in Method 1 to provide the crude product which was used without further purification. LC/MS *m/z* 194.1 (MH⁺), *R*_t 1.199 minutes.

WO 02/18383

PCT/US01/41942

-81-

Method 4

To a stirred NMP solution containing NaH (1.3 eq) was added an alcohol (1.0 eq), e.g. 2-methoxyethanol. The resulting mixture was then stirred
5 for 30 minutes. A slurry of 5-fluoro-2-nitrophenylamine in NMP was then added slowly. The mixture was then heated to 100°C. After 2 hours, the reaction mixture was cooled and water was added. The mixture was then filtered and the captured solid was washed with water and purified by silica gel chromatography (1:1 ethyl acetate:hexane). LC/MS m/z 213.2 (MH⁺), R_t 2.24 minutes. The
10 nitroamine was reduced as in Method 1 to provide the crude product which was used without further purification. LC/MS m/z 183.1 (MH⁺), R_t 0.984 minutes.

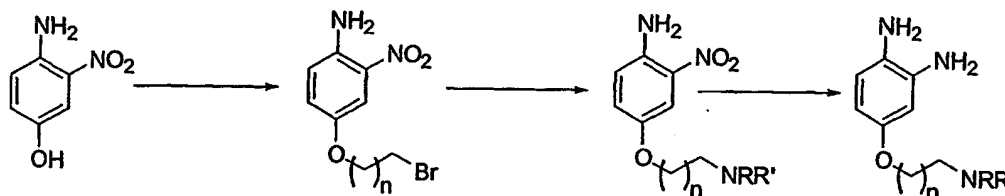
Method 5

Diisopropyl azodicarboxylate (1.1 eq) was added dropwise to a
15 stirred solution of 4-amino-3-nitrophenol (1.0 eq), triphenylphosphine (1.1 eq), and an alcohol, e.g. N-(2-hydroxyethyl)morpholine (1.0 eq), in tetrahydrofuran at 0°C. The mixture was allowed to warm to room temperature and stirred for 18 hours. The solvent was evaporated, and the product was purified by silica gel chromatography (98:2 CH₂Cl₂:methanol) to yield 4-(2-morpholin-4-ylethoxy)-2-
20 nitrophenylamine as a dark reddish-brown oil. LC/MS m/z 268.0 (MH⁺), R_t 1.01 minutes. The nitroamine was reduced as in Method 1 to give the crude product which was used without further purification. LC/MS m/z 238.3 (MH⁺), R_t 0.295 minutes.

WO 02/18383

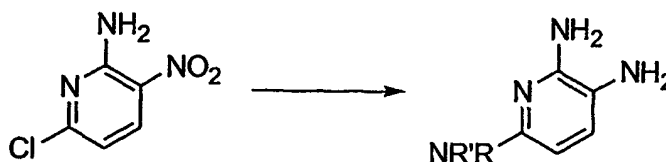
PCT/US01/41942

-82-

Method 6

- To a flask charged with 4-amino-3-nitrophenol (1 eq), K_2CO_3 (2 eq),
 5 and 2-butanone was added an alkyl dibromide, e.g. 1,3-dibromopropane
 (1.5 eq). The resulting mixture was then heated at $80^\circ C$ for 18 hours. After
 cooling, the mixture was filtered, concentrated, and diluted with water. The
 solution was then extracted with CH_2Cl_2 (3 x) and the combined organic layers were
 concentrated to give a solid that was then washed with pentane. LCMS m/z 275.1
 10 (MH⁺), R_t 2.74 minutes.

- An acetonitrile solution of the bromide prepared above, an amine,
 e.g. pyrrolidine (5 eq), Cs_2CO_3 (2 eq) and Bu_4NI (0.1 eq) was heated at $70^\circ C$ for
 48 hours. The reaction mixture was cooled, filtered, and concentrated. The
 residue was dissolved in CH_2Cl_2 , washed with water, and concentrated to give the
 15 desired nitroamine, 2-nitro-4-(3-pyrrolidin-1-ylpropoxy)phenylamine. LCMS m/z
 266.2 (MH⁺), R_t 1.51 minutes. The nitroamine was reduced as in Method 1 to
 provide the crude product which was used without further purification.

Method 7

- 20 To a suspension of 6-chloro-3-nitropyridin-2-amine (1 eq) in
 acetonitrile was added an amine, e.g. morpholine (4 eq). The resulting reaction
 mixture was stirred at $70^\circ C$ for 5 hours. The solvent was evaporated under

WO 02/18383

PCT/US01/41942

-83-

reduced pressure, and the residue triturated with ether to provide the desired compound as a bright yellow powder. LC/MS m/z 225.0 (MH⁺), R_t 1.79 minutes. The nitroamine was reduced as in Method 1 to provide the crude product which was used without further purification.

5

Example 1

3-[2-(Methoxycarbonyl)acetylamino]pyridine-4-carboxylic acid

A solution of 3-aminopyridine-4-carboxylic acid (1.0 eq), methyl 2-(chlorocarbonyl)acetate (1.1 eq), and triethylamine (2.0 eq) in acetone was stirred overnight at room temperature. The solvent was removed *in vacuo*. The product
10 was used without further purification. LC/MS m/z 239.2 (MH⁺), R_t 1.40 minutes.

3-Benzimidazol-2-yl-4-hydroxyhydropyridino[3,4-b]pyridin-2-one

3-[2-(Methoxycarbonyl)acetylamino]pyridine-4-carboxylic acid (1.1 eq) was combined with 1,2-phenylenediamine (1.0 eq) and heated at 150°C for 3 hours. The crude product was purified by reversed-phase HPLC (DMSO/ 5%
15 TFA). LC/MS m/z 279.3 (MH⁺), R_t 1.73 minutes.

Example 2

4-Hydroxy-3-(5-methylbenzimidazol-2-yl)hydropyridino[3,4-b]pyridin-2-one

The title compound was synthesized as described in Example 1 using 3-[2-(methoxycarbonyl)acetylamino]-pyridine-4-carboxylic acid and 4-methyl-1,2-
20 phenylenediamine. The crude product was purified by reversed-phase HPLC (DMSO/ 5% TFA). LC/MS m/z 293.3 (MH⁺), R_t 1.99 minutes.

WO 02/18383

PCT/US01/41942

-84-

Example 3**Ethyl 2-benzimidazol-2-ylacetate**

- A solution of 1,2-phenylenediamine (1.0 eq) and ethyl 3-ethoxy-3-iminopropanoate hydrochloride (1.3 eq) in EtOH was stirred at 90°C overnight.
- 5 The reaction was cooled to room temperature and the solvent removed *in vacuo*. Water and CH₂Cl₂ were added to the residue. The organic layer was separated, dried over Na₂SO₄ and the solvent removed. The solid recovered was used without purification. LC/MS *m/z* 205.2 (MH⁺), R_t 1.44 minutes.

Method A

10 **2-Benzimidazol-2-yl-N-(4-cyano(3-pyridyl))acetamide**

- LiHMDS (2.5 eq) was added to ethyl 2-benzimidazol-2-ylacetate (1.0 eq) in THF at -78°C. After 1 hour, 3-amino-4-cyanopyridine (0.8 eq) in THF was added. The resulting mixture was allowed to warm to room temperature overnight. The mixture was quenched with NH₄Cl (aqueous saturated solution) and extracted
- 15 with EtOAc. The organic layer washed with H₂O and brine, dried over Na₂SO₄, filtered, and concentrated *in vacuo* to yield a brown solid. The crude material was purified by silica gel chromatography (5:1 EtOAc:hexane) to yield the desired product. LC/MS *m/z* 278.3 (MH⁺), R_t 1.88 minutes.

4-Amino-3-benzimidazol-2-ylhydropyridino[3,4-b]pyridin-2-one

- 20 2-Benzimidazol-2-yl-N-(4-cyano(3-pyridyl))acetamide (1.0 eq) was heated in NaOMe (18 eq, 0.5 M in MeOH) at 70°C for 2 hours. The reaction mixture was cooled, and the resulting solid was filtered and washed with water to provide the desired product. LC/MS *m/z* 278.3 (MH⁺), R_t 1.91 minutes.

WO 02/18383

PCT/US01/41942

-85-

Example 4

Ethyl 2-(5-methylbenzimidazol-2-yl)acetate

The title compound was synthesized as described in Example 3 using 4-methyl-1,2-phenylenediamine. LC/MS m/z 219.3 (MH⁺), R_t 1.60 minutes.

5 *N*-(4-Cyano(3-pyridyl))-2-(5-methylbenzimidazol-2-yl)acetamide

The title compound was synthesized as described in Example 3, Method A using ethyl 2-(5-methylbenzimidazol-2-yl)acetate. LC/MS m/z 292.4 (MH⁺), R_t 1.71 minutes.

4-Amino-3-(5-methylbenzimidazol-2-yl)hydropyridino[3,4-b]pyridin-2-one

10 The title compound was synthesized as described in Example 3, Method A using *N*-(4-cyano(3-pyridyl))-2-(5-methylbenzimidazol-2-yl)acetamide. LC/MS m/z 292.4 (MH⁺), R_t 2.04 minutes.

Example 5

4-(2-Morpholin-4-ylethoxy)-2-nitrophenylamine

15 Diisopropyl azodicarboxylate (1.1 eq) was added dropwise to a stirred solution of 4-amino-3-nitrophenol (1.0 eq), triphenylphosphine (1.1 eq), and *N*-(2-hydroxyethyl)morpholine (1.0 eq), in THF at 0°C. The mixture was allowed to warm to room temperature and left to stir for 18 hours. The solvent was evaporated and the product was purified by silica gel chromatography (98:2
20 CH₂Cl₂:MeOH) to yield a dark reddish-brown oil. LC/MS m/z 268.0 (MH⁺), R_t 1.01 minutes.

4-(2-Morpholin-4-ylethoxy)benzene-1,2-diamine

To a solution 4-(2-morpholin-4-ylethoxy)-2-nitrophenylamine (1.0 eq) in EtOH was added Pd/C (0.1 eq). The reaction vessel was repeatedly purged

WO 02/18383

PCT/US01/41942

-86-

with nitrogen, then stirred under a hydrogen atmosphere (1 atm) for 18 hours. The product was filtered through a Celite plug, and the plug washed with EtOH. The diamine was used without purification. LC/MS m/z 238.3 (MH⁺), R_t 0.295 minutes.

5 **Ethyl 2-[5-(2-morpholin-4-ylethoxy)benzimidazol-2-yl]acetate**

The title compound was synthesized as described in Example 3 using 4-(2-morpholin-4-ylethoxy)benzene-1,2-diamine. The organic layer was concentrated and the residue purified by silica gel chromatography (10:1:2 CH₂Cl₂:MeOH:EtOAc) to yield a dark reddish brown oil. LC/MS m/z 334.4 (MH⁺), R_t 1.08 minutes.

***N*-(4-Cyano(3-pyridyl))-2-[5-(2-morpholin-4-ylethoxy)benzimidazol-2-yl]acetamide**

The title compound was synthesized as described in Example 3, Method A using ethyl 2-[5-(2-morpholin-4-ylethoxy)benzimidazol-2-yl]acetate.

15 LC/MS m/z 407.4 (MH⁺), R_t 1.25 minutes.

4-Amino-3-[5-(2-morpholin-4-ylethoxy)benzimidazol-2-yl]hydropyridino[3,4-b]pyridin-2-one

The title compound was synthesized as described in Example 3, Method A using *N*-(4-cyano(3-pyridyl))-2-[5-(2-morpholin-4-ylethoxy)benzimidazol-2-yl]acetamide. LC/MS m/z 407.4 (MH⁺), R_t 1.41 minutes.

20

Example 6

2-[(Ethoxycarbonyl)methyl]benzimidazole-5-carboxylic acid

The title compound was synthesized as described in Example 3 using 3,4-diaminobenzoic acid. The crude material was purified by silica gel

25

WO 02/18383

PCT/US01/41942

-87-

chromatography (0-5% MeOH/CH₂Cl₂) to afford the desired product as a white to off-white solid. LC/MS *m/z* 249.1 (MH⁺), R_t 1.35 minutes.

Ethyl 2-[5-(N,N-dimethylcarbamoyl)benzimidazol-2-yl]acetate

2-[(Ethoxycarbonyl)methyl]benzimidazole-5-carboxylic acid (1.0 eq)
5 was dissolved in THF. HBTU (1.1 eq) and diisopropylethylamine (2.0 eq) were added, followed by dimethylamine (2.0 M in THF, 1.1 eq). The reaction was stirred at room temperature overnight then concentrated and the residue was purified by silica gel chromatography (5:95 MeOH/CH₂Cl₂) to afford the desired compound. LC/MS *m/z* 276.2 (MH⁺), R_t 1.18 minutes.

10 Method B

[2-(4-Amino-2-oxohydropyridino[3,4-b]pyridin-3-yl)benzimidazol-5-yl]-N,N-dimethylcarboxamide

Ethyl 2-[5-(N,N-dimethylcarbamoyl)benzimidazol-2-yl]acetate (1.0 eq) and anthranilonitrile (1.0 eq) were dissolved in 1,2-dichloroethane, and then
15 SnCl₄ (5.5 eq) was added. The mixture was heated at reflux overnight. Upon cooling, the mixture was concentrated *in vacuo*. NaOH (3 M) was added to the solid, and the mixture heated at 80°C for 0.5 hours. The solid was filtered and washed sequentially with H₂O, CH₂Cl₂, and acetone. LC/MS indicated that the product was present in the acetone layer and the solid. These fractions were
20 combined and purified by silica gel chromatography (5-10% MeOH in CH₂Cl₂ with 1% Et₃N) to give the desired product. LC/MS *m/z* 349.3 (MH⁺), R_t 1.68 minutes.

Example 7

5-Fluoro-2-nitrophenylamine

2,4-Difluoronitrobenzene (1.0 eq) was placed in a dry round-
25 bottomed flask equipped with a dry ice condenser charged with acetone/dry ice. Ammonia was condensed into the flask and the resulting solution was stirred at

WO 02/18383

PCT/US01/41942

-88-

reflux for 7 hours. A yellow precipitate was formed within 1 hour. After 7 hours, the condenser was removed and the liquid ammonia was allowed to evaporate over several hours. The crude product was purified by flash chromatography on silica gel (85:15 hexanes:EtOAc, product at $R_f = 0.32$, contaminant at $R_f = 0.51$). GC/MS
5 m/z 156.1 (M+), R_t 11.16 minutes.

5-Morpholin-4-yl-2-nitrophenylamine

5-Fluoro-2-nitrophenylamine (1.0 eq) and morpholine (3.0 eq) were dissolved in NMP and heated at 100°C for 1 hour. The solution was cooled to room temperature and diluted with water. The resulting precipitate was filtered and
10 dried under vacuum to yield 5-morpholin-4-yl-2-nitrophenylamine. The resulting solid was recrystallized from EtOH to afford pure product as a bright yellow solid. LC/MS m/z 224.1 (MH+), R_t 1.89 minutes.

Ethyl 2-(5-morpholin-4-ylbenzimidazol-2-yl)acetate

The title compound was synthesized as described in Example 5 using
15 5-morpholin-4-yl-2-nitrophenylamine. The crude yellow oil was purified by flash column chromatography (89.5:10:0.5 CH₂Cl₂:MeOH:Et₃N) to yield pure product as a yellow solid. LC/MS m/z 290.3 (MH+), R_t 1.31 minutes.

4-Amino-3-(5-morpholin-4-ylbenzimidazol-2-yl)hydropyridino[3,4-b]pyridin-2-one

20 The title compound was synthesized as described in Example 6, Method B using ethyl 2-(5-morpholin-4-ylbenzimidazol-2-yl)acetate. LC/MS m/z 363.2 (MH+), R_t 1.60 minutes.

WO 02/18383

PCT/US01/41942

-89-

Example 8**[1-(3-Amino-4-nitrophenyl)pyrrolidin-3-yl]dimethylamine**

The title compound was synthesized as described in Example 7 using 3-(dimethylamino)pyrrolidine. LC/MS *m/z* 251.3 (MH⁺), R_t 1.25 minutes.

5 Ethyl 2-{5-[3-(dimethylamino)pyrrolidinyl]benzimidazol-2-yl}acetate

The title compound was synthesized as described in Example 5 using [1-(3-amino-4-nitrophenyl)pyrrolidin-3-yl]dimethylamine and the resulting diamine was used according to Example 3 to form the benzimidazole. The product was obtained as a yellow oil. LC/MS *m/z* 317.4 (MH⁺), R_t 1.36 minutes.

10 4-Amino-3-{5-[3-(dimethylamino)pyrrolidinyl]benzimidazol-2-yl}hydropyridino[3,4-b]pyridin-2-one

The title compound was synthesized as described in Example 6, Method B using ethyl 2-[5-(dimethylamino)benzimidazol-2-yl]acetate. LC/MS *m/z* 390.2 (MH⁺), R_t 1.45 minutes.

15 Example 9**3H-Imidazo[4,5-b]pyridin-2-ylacetonitrile**

Ethyl cyanoacetate (1.5 eq) and 2,3-diaminopyridine (1 eq) were heated at 185°C for 30 minutes. The reaction mixture was cooled to room temperature and the black solid was triturated with ether. The desired product was
20 thus obtained as a dark brown powder. LC/MS *m/z* 159.1 (MH⁺), R_t 0.44 minutes.

Ethyl 3H-imidazo[4,5-b]pyridin-2-ylacetate

3H-Imidazo[4,5-b]pyridin-2-ylacetonitrile was suspended in EtOH, and gaseous HCl was bubbled through for 3 hours. The suspension initially
25 dissolved, but a precipitate started forming almost immediately. The reaction

WO 02/18383

PCT/US01/41942

-90-

mixture was cooled to 0°C and a cold saturated NaHCO₃ solution was carefully added. Solid NaHCO₃ was also added until a pH of 7.6 was achieved. The aqueous phase was then extracted with EtOAc, and the organic extracts were dried (Na₂SO₄). After evaporation of the solvent under reduced pressure, the residue was
5 purified by chromatography on silica gel (10% MeOH in CH₂Cl₂ with 1% Et₃N) providing the desired product as a light brown solid. LC/MS *m/z* 206.1 (MH⁺), R_t 0.97 minutes.

4-Amino-3-(3H-imidazo[4,5-b]pyridin-2-yl)-1,7-naphthyridin-2(1H)-one

LiHMDS (3.0 eq) was added to ethyl 3H-imidazo[4,5-b]pyridin-2-ylacetate (1.0 eq) in THF at -78°C. After 20 minutes, a solution of 3-aminopyridine-4-carbonitrile (1.1 eq) in THF was added. The resulting mixture was allowed to warm to room temperature, stirred 3 hours, and then refluxed overnight. The mixture was cooled to 0 °C and quenched with an aqueous saturated NH₄Cl solution. A precipitate formed, was filtered off, and was washed
15 repeatedly with ether to yield the desired compound as a brown solid. Purification by reverse phase chromatography afforded the desired product as a yellow solid. LC/MS *m/z* 279.0 (MH⁺), R_t 1.29 minutes.

Example 10

20 4-Amino-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1,7-naphthyridin-2(1H)-one

LiHMDS (3.6 eq) was added to ethyl [5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]acetate (1.0 eq) and 3-aminopyridine-4-carbonitrile (1.0 eq) in THF at 0°C. The reaction was stirred overnight. The resulting mixture was quenched with an aqueous saturated NH₄Cl solution and extracted with EtOAc. The
25 combined organic layers were washed with H₂O and brine, dried over Na₂SO₄, filtered, and concentrated *in vacuo* to yield a green solid. The crude material was washed successively with CH₂Cl₂ and MeOH and then was purified by reverse

WO 02/18383

PCT/US01/41942

-91-

phase HPLC to provide the desired product. LC/MS m/z 376.3 (MH⁺), R_t 1.70 minutes.

Example 11

5 4-Amino-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)-1,6-naphthyridin-2(1H)-one

LiHMDS (3.3 eq) was added to ethyl (5-morpholin-4-yl-1H-benzimidazol-2-yl)acetate (1.0 eq) and 4-aminopyridine-3-carbonitrile (see J. Chem. Soc. 1967, p1558-1564; 1.0 eq) in THF at 0°C. The reaction was stirred overnight. The resulting mixture was quenched with an aqueous saturated NH₄Cl solution and extracted with EtOAc. The combined organic layers were washed with H₂O and brine, dried over Na₂SO₄, filtered, and concentrated *in vacuo* to yield a brown solid. The crude material was washed successively with CH₂Cl₂ and MeOH, and then was purified by reverse phase HPLC to provide the desired product. LC/MS m/z 363.2 (MH⁺), R_t 1.55 minutes.

15

Example 12

4-Amino-3-{5-[3-(dimethylamino)pyrrolidin-1-yl]-1H-benzimidazol-2-yl}-1,5-naphthyridin-2(1H)-one

LiHMDS (3.6 eq) was added to ethyl {5-[3-(dimethylamino)pyrrolidin-1-yl]-1H-benzimidazol-2-yl}acetate (1.0 eq) and 3-aminopyridine-2-carbonitrile (J. Org. Chem. 1958, 1616-1617; 1.0 eq) in THF at 0°C. The reaction was stirred overnight and then heated at 40°C for 3 hours. The resulting mixture was quenched with an aqueous saturated NH₄Cl solution and extracted with EtOAc. The combined organic layers were washed with H₂O and brine, dried over Na₂SO₄, filtered, and concentrated *in vacuo* to yield a green solid. The crude material was washed successively with CH₂Cl₂ and MeOH, and then was purified by reverse phase HPLC to provide the desired product. LC/MS m/z 390.2 (MH⁺), R_t 1.79 minutes.

WO 02/18383

PCT/US01/41942

-92-

Example 13**4-Amino-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1,5-naphthyridin-2(1H)-one**

LiHMDS (3.6 eq) was added to ethyl [5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]acetate (1.0 eq) and 3-aminopyridine-2-carbonitrile (1.0 eq) in THF at 0°C. The reaction was stirred overnight and then heated at 40°C for 3 hours. The resulting mixture was quenched with an aqueous saturated NH₄Cl solution and extracted with EtOAc. The combined organic layers were washed with H₂O and brine, dried over Na₂SO₄, filtered, and concentrated *in vacuo* to yield a green solid. The crude material was washed successively with CH₂Cl₂ and MeOH, and then was purified by reverse phase HPLC to provide the desired product. LC/MS *m/z* 376.1 (MH⁺), R_t 1.50 minutes.

Example 14**3-(1H-Benzimidazol-2-yl)-4-hydroxy-1,8-naphthyridin-2(1H)-one**

The synthesis of the title compound is outlined in Scheme 5.

Example 15**2-(1H-Benzimidazol-2-yl)-N-(4-cyano-1H-pyrazol-5-yl)acetamide**

LiHMDS (4.3 eq) was added to ethyl 1H-benzimidazol-2-ylacetate (1.0 eq) 5-amino-1H-pyrazole-4-carbonitrile (1.0 eq) in THF at 0°C. After 1 hour, the resulting mixture was warmed to room temperature, stirred overnight, and then heated at 40°C for 4 hours. The mixture was quenched with an aqueous saturated NH₄Cl solution and extracted with EtOAc. The organic layer was washed with H₂O and brine, dried over Na₂SO₄, filtered, and concentrated *in vacuo* to yield a tan solid. LC/MS *m/z* 267.1 (MH⁺), R_t 1.37 minutes.

WO 02/18383

PCT/US01/41942

-93-

4-Amino-5-(1H-benzimidazol-2-yl)-1,7-dihydro-6H-pyrazolo[3,4-b]pyridin-6-one

2-(1H-Benzimidazol-2-yl)-N-(4-cyano-1H-pyrazol-5-yl)acetamide (1.0 eq) was heated in NaOMe (20 eq, 0.5 M in MeOH) at 100°C for 2 days. H₂O was added, and the mixture was extracted with EtOAc. The organic layer was
5 washed with H₂O and brine, dried over Na₂SO₄, filtered, and concentrated *in vacuo* to yield a solid. The material was purified by reverse phase HPLC. LC/MS *m/z* 267.1 (MH⁺), R_t 1.57 minutes.

Example 16**4-Amino-5-(1H-benzimidazol-2-yl)thieno[2,3-b]pyridin-6(7H)-one**

10 LiHMDS (4.3 eq) was added to ethyl 1H-benzimidazol-2-ylacetate (1.1 eq) and 2-aminothiophene-3-carbonitrile (1.0 eq) in THF at 0°C. After 1 hour, the resulting mixture was warmed to room temperature and then stirred overnight. The mixture was quenched with an aqueous saturated NH₄Cl solution and extracted with EtOAc. The organic layer was washed with H₂O and brine,
15 dried over Na₂SO₄, filtered, and concentrated *in vacuo* to yield a brown solid. LC/MS *m/z* 283.1 (MH⁺), R_t 1.88 minutes.

Example 17**7-Amino-6-(1H-benzimidazol-2-yl)-3,4-dihydro-5H-imidazo[4,5-b]pyridin-5-one**

LiHMDS (4.4 eq) was added to ethyl 1H-benzimidazol-2-ylacetate
20 (1.0 eq) and 5-amino-1H-imidazole-4-carbonitrile (1.0 eq) in THF at 0°C. After 1 hour, the resulting mixture was warmed to room temperature and then stirred overnight. The mixture was quenched with an aqueous saturated NH₄Cl solution and extracted with EtOAc. The organic layer was washed with H₂O and brine, dried over Na₂SO₄, filtered, and concentrated *in vacuo* to yield a brown solid.
25 LC/MS *m/z* 267.1 (MH⁺), R_t 1.47 minutes.

WO 02/18383

PCT/US01/41942

-94-

Example 18

4-Amino-5-(1H-benzimidazol-2-yl)-1-methyl-1,7-dihydro-6H-pyrazolo[3,4-b]pyridin-6-one

5-Amino-1-methyl-1H-pyrazole-4-carbonitrile (1.0 eq) and ethyl 1H-benzimidazol-2-ylacetate (1.0 eq) were dissolved in THF and dried over sieves. LiHMDS (3 eq) was added dropwise and the mixture stirred for 18 hours. The mixture was filtered and diluted with EtOAc, then washed with an aqueous saturated NH₄Cl solution. The aqueous layer was washed with EtOAc (3x), and the organic layers combined, dried over MgSO₄, and concentrated yielding pure product. LC/MS *m/z* 281.0 (MH⁺), *R_t* 1.41 minutes.

Assay Procedures

In vitro kinase assays for receptor tyrosine kinases

The kinase activity of various protein tyrosine kinases can be measured by providing ATP and a suitable peptide or protein tyrosine-containing substrate, and assaying the transfer of phosphate moiety to the tyrosine residue. Recombinant proteins corresponding to the cytoplasmic domains of the flt-1 (VEGFR1), KDR (VEGFR2), and bFGF receptors were expressed in Sf9 insect cells using a Baculovirus expression system (InVitrogen) and purified via Glu antibody interaction (for Glu-epitope tagged constructs) or by Metal Ion Chromatography (for His₆ tagged constructs). For each assay, test compounds were serially diluted in DMSO then mixed with an appropriate kinase reaction buffer plus ATP. Kinase protein and an appropriate biotinylated peptide substrate were added to give a final volume of 100 μ L, reactions were incubated for 1-2 hours at room temperature and stopped by the addition of 50 μ L of 45mM EDTA, 50mM Hepes pH 7.5. Stopped reaction mix (75 μ L) was transferred to a streptavidin coated microtiter plate (Boehringer Mannheim) and incubated for 1 hour. Phosphorylated peptide product was measured with the DELFIA time-resolved fluorescence system (Wallac), using a Eu-labeled anti-phosphotyrosine antibody PT66 with the

WO 02/18383

PCT/US01/41942

-95-

modification that the DELFIA assay buffer was supplemented with 1 mM MgCl₂ for the antibody dilution. Time resolved fluorescence was read on a Wallac 1232 DELFIA fluorometer. The concentration of each compound for 50% inhibition (IC₅₀) was calculated by non-linear regression using XL Fit data analysis software.

5 Flt-1, KDR, and bFGFR kinases were assayed in 50 mM Hepes pH 7.0, 2 mM MgCl₂, 10 mM MnCl₂, 1 mM NaF, 1 mM DTT, 1 mg/ml BSA, 2 μM ATP, and 0.42 μM biotin-GGGGQDGKDYIVLPI-NH₂. Flt-1, KDR, and bFGFR kinases were added at 0.1 μg/mL, 0.05 μg/mL, or 0.1 μg/mL respectively.

10 Each of the following compounds was synthesized and assayed using the procedures described above:

- 4-(1-azabicyclo[2.2.2]oct-3-ylamino)-3-(1H-benzimidazol-2-yl)-6-fluoro-1,7-naphthyridin-2(1H)-one;
- 4-(1-azabicyclo[2.2.2]oct-3-ylamino)-3-(1H-benzimidazol-2-yl)-6-chloro-1,7-naphthyridin-2(1H)-one;
- 15 3-benzimidazol-2-yl-4-hydroxyhydropyridino[3,4-b]pyridin-2-one;
- 4-hydroxy-3-(5-methylbenzimidazol-2-yl)hydropyridino[3,4-b]pyridin-2-one;
- 4-amino-3-benzimidazol-2-ylhydropyridino[3,4-b]pyridin-2-one;
- 4-amino-3-(5-methylbenzimidazol-2-yl)hydropyridino[3,4-b]pyridin-2-one;
- 4-amino-3-[5-(2-morpholin-4-ylethoxy)benzimidazol-2-yl]hydropyridino[3,4-b]pyridin-2-one;
- 20 [2-(4-amino-2-oxohydropyridino[3,4-b]pyridin-3-yl)benzimidazol-5-yl]-N,N-dimethylcarboxamide;
- 4-amino-3-(5-morpholin-4-ylbenzimidazol-2-yl)hydropyridino[3,4-b]pyridin-2-one;
- 4-amino-3-{5-[3-(dimethylamino)pyrrolidinyl]benzimidazol-2-yl}hydropyridino[3,4-b]pyridin-2-one;
- 25 4-amino-3-(3H-imidazo[4,5-b]pyridin-2-yl)-1,7-naphthyridin-2(1H)-one;

WO 02/18383

PCT/US01/41942

-96-

- 4-amino-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1,7-naphthyridin-2(1H)-one;
- 4-amino-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)-1,6-naphthyridin-2(1H)-one;
- 4-amino-3-{5-[3-(dimethylamino)pyrrolidin-1-yl]-1H-benzimidazol-2-yl}-1,5-naphthyridin-2(1H)-one;
- 5 4-amino-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1,5-naphthyridin-2(1H)-one;
- 4-amino-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1,5-naphthyridin-2(1H)-one;
- 3-(1H-benzimidazol-2-yl)-4-hydroxy-1,8-naphthyridin-2(1H)-one;
- 4-amino-5-(1H-benzimidazol-2-yl)-1,7-dihydro-6H-pyrazolo[3,4-b]pyridin-6-one;
- 10 4-amino-5-(1H-benzimidazol-2-yl)thieno[2,3-b]pyridin-6(7H)-one;
- 7-amino-6-(1H-benzimidazol-2-yl)-3,4-dihydro-5H-imidazo[4,5-b]pyridin-5-one;
- and
- 4-amino-5-(1H-benzimidazol-2-yl)-1-methyl-1,7-dihydro-6H-pyrazolo[3,4-b]pyridin-6-one.

- 15 Each of the above compounds displayed an IC₅₀ value of less than 10 µM with respect to VEGFR1, KDR, and bFGF.

- It should be understood that the organic compounds according to the invention may exhibit the phenomenon of tautomerism. As the chemical structures within this specification can only represent one of the possible tautomeric forms, it
- 20 should be understood that the invention encompasses any tautomeric form of the drawn structure.

It is understood that the invention is not limited to the embodiments set forth herein for illustration, but embraces all such forms thereof as come within the scope of the following claims.

WO 02/18383

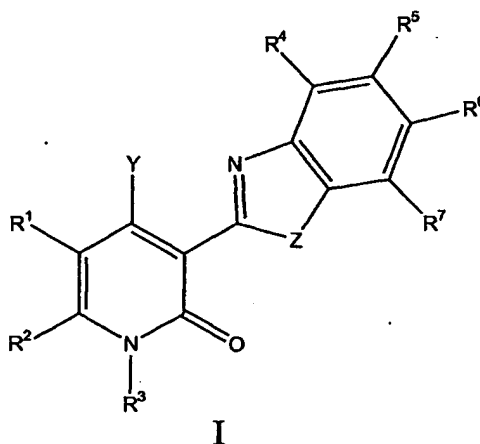
PCT/US01/41942

-97-

CLAIMS

What is claimed is:

1. A compound having the structure I, a tautomer of the compound, a pharmaceutically acceptable salt of the compound, or a pharmaceutically acceptable salt of the tautomer



4

5

wherein,

- 6 Y is selected from the group consisting of -OH, -OR⁸ groups, -SH,
- 7 -SR⁹ groups, -NR¹⁰R¹¹ groups, -CN, -C(=O)-R¹² groups, substituted
- 8 and unsubstituted alkyl groups, substituted and unsubstituted alkenyl
- 9 groups, substituted and unsubstituted alkynyl groups, substituted and
- 10 unsubstituted aralkyl groups, substituted and unsubstituted
- 11 heterocyclalkyl groups, substituted and unsubstituted
- 12 alkylaminoalkyl groups, substituted and unsubstituted
- 13 dialkylaminoalkyl groups, substituted and unsubstituted
- 14 arylaminoalkyl groups, substituted and unsubstituted
- 15 diarylaminoalkyl groups, substituted and unsubstituted
- 16 (alkyl)(aryl)aminoalkyl groups, substituted and unsubstituted

WO 02/18383

PCT/US01/41942

-98-

- 17 heterocyclylaminoalkyl groups, substituted and unsubstituted
18 diheterocyclylaminoalkyl groups, substituted and unsubstituted
19 (alkyl)(heterocyclyl)aminoalkyl groups, substituted and unsubstituted
20 (aryl)(heterocyclyl)aminoalkyl groups, substituted and unsubstituted
21 heterocyclyl groups, substituted and unsubstituted aryl groups,
22 substituted and unsubstituted hydroxyalkyl groups, substituted and
23 unsubstituted alkoxyalkyl groups, substituted and unsubstituted
24 aryloxyalkyl groups, and substituted and unsubstituted
25 heterocyclyloxyalkyl groups;
- 26 Z is selected from the group consisting of O, S, and NR¹³ groups;
- 27 R¹ and R² join to form a 5 to 7 membered substituted or unsubstituted
28 ring comprising at least one O, N, or S atom;
- 29 R³ and R¹³ may be the same or different and are selected from the
30 group consisting of H, -OH, substituted and unsubstituted alkoxy
31 groups, substituted and unsubstituted aryloxy groups, -NH₂,
32 substituted and unsubstituted alkylamino groups, substituted and
33 unsubstituted arylamino groups, substituted and unsubstituted
34 dialkylamino groups, substituted and unsubstituted diarylamino
35 groups, substituted and unsubstituted (alkyl)(aryl)amino groups,
36 substituted and unsubstituted heterocyclylamino groups, substituted
37 and unsubstituted diheterocyclylamino groups, substituted and
38 unsubstituted (alkyl)(heterocyclyl)amino groups, substituted and
39 unsubstituted (aryl)(heterocyclyl)amino groups, substituted and
40 unsubstituted heterocyclyloxy groups, substituted and unsubstituted
41 alkyl groups, substituted and unsubstituted aryl groups, -C(=O)H,
42 -C(=O)-alkyl groups, and -C(=O)-aryl groups;

WO 02/18383

PCT/US01/41942

-99-

43 R^4 , R^5 , R^6 , and R^7 may be the same or different and are
44 independently selected from the group consisting of H, Cl, Br, F, I,
45 $-NO_2$, $-CN$, $-OH$, $-OR^{14}$ groups, $-NR^{15}R^{16}$ groups, $-C(=O)R^{17}$
46 groups, $-SH$, $-SR^{18}$ groups, $-S(=O)R^{19}$ groups, $S(=O)_2R^{20}$ groups,
47 substituted and unsubstituted amidinyl groups, substituted and
48 unsubstituted guanidinyl groups, substituted and unsubstituted
49 primary, secondary, and tertiary alkyl groups, substituted and
50 unsubstituted aryl groups, substituted and unsubstituted alkenyl
51 groups, substituted and unsubstituted alkynyl groups, substituted and
52 unsubstituted heterocyclyl groups, substituted and unsubstituted
53 alkylaminoalkyl groups, substituted and unsubstituted
54 dialkylaminoalkyl groups, substituted and unsubstituted
55 arylaminoalkyl groups, substituted and unsubstituted
56 diarylaminoalkyl groups, substituted and unsubstituted
57 (alkyl)(aryl)aminoalkyl groups, substituted and unsubstituted
58 heterocyclylalkyl groups, substituted and unsubstituted aminoalkyl
59 groups, substituted and unsubstituted heterocyclylaminoalkyl groups,
60 substituted and unsubstituted diheterocyclylaminoalkyl groups,
61 substituted and unsubstituted (alkyl)(heterocyclyl)aminoalkyl groups,
62 substituted and unsubstituted (aryl)(heterocyclyl)aminoalkyl groups,
63 substituted and unsubstituted hydroxyalkyl groups, substituted and
64 unsubstituted alkoxyalkyl groups, substituted and unsubstituted
65 aryloxyalkyl groups, and substituted and unsubstituted
66 heterocycloxyalkyl groups;

67 R^8 is selected from the group consisting of substituted and
68 unsubstituted alkyl groups, substituted and unsubstituted aryl groups,
69 substituted and unsubstituted heterocyclyl groups, substituted and
70 unsubstituted heterocyclylalkyl groups, $-C(=O)H$, $-C(=O)$ -alkyl
71 groups, $-C(=O)$ -aryl groups, $-C(=O)O$ -alkyl groups, $-C(=O)O$ -aryl

WO 02/18383

PCT/US01/41942

-100-

- 72 groups, -C(=O)NH₂, -C(=O)NH(alkyl) groups, -C(=O)NH(aryl)
73 groups, -C(=O)N(alkyl)₂ groups, -C(=O)N(aryl)₂ groups,
74 -C(=O)N(alkyl)(aryl) groups, -NH₂, -NH(alkyl) groups, -NH(aryl)
75 groups, -N(alkyl)₂ groups, -N(alkyl)(aryl) groups, -N(aryl)₂ groups,
76 -C(=O)NH(heterocyclyl) groups, -C(=O)N(heterocyclyl)₂ groups,
77 -C(=O)N(alkyl)(heterocyclyl) groups, and
78 -C(=O)N(aryl)(heterocyclyl) groups;
- 79 R⁹ and R¹⁸ may be the same or different and are independently
80 selected from the group consisting of substituted and unsubstituted
81 alkyl groups, and substituted and unsubstituted aryl groups;
- 82 R¹⁰ is selected from the group consisting of H, substituted and
83 unsubstituted alkyl groups, substituted and unsubstituted aryl groups,
84 and substituted and unsubstituted heterocyclyl groups;
- 85 R¹¹ is selected from the group consisting of H, substituted and
86 unsubstituted alkyl groups, substituted and unsubstituted aryl groups,
87 substituted and unsubstituted heterocyclyl groups, -OH, alkoxy
88 groups, aryloxy groups, -NH₂, substituted and unsubstituted
89 heterocyclylalkyl groups, substituted and unsubstituted aminoalkyl
90 groups, substituted and unsubstituted alkylaminoalkyl groups,
91 substituted and unsubstituted dialkylaminoalkyl groups, substituted
92 and unsubstituted arylaminoalkyl groups, substituted and
93 unsubstituted diarylaminoalkyl groups, substituted and unsubstituted
94 (alkyl)(aryl)aminoalkyl groups, substituted and unsubstituted
95 alkylamino groups, substituted and unsubstituted arylamino groups,
96 substituted and unsubstituted dialkylamino groups, substituted and
97 unsubstituted diarylamino groups, substituted and unsubstituted
98 (alkyl)(aryl)amino groups, -C(=O)H, -C(=O)-alkyl groups,

WO 02/18383

PCT/US01/41942

-101-

- 99 -C(=O)-aryl groups, -C(=O)O-alkyl groups, -C(=O)O-aryl groups,
100 -C(=O)NH₂, -C(=O)NH(alkyl) groups, -C(=O)NH(aryl) groups,
101 -C(=O)N(alkyl)₂ groups, -C(=O)N(aryl)₂ groups,
102 -C(=O)N(alkyl)(aryl) groups, -C(=O)-heterocyclyl groups,
103 -C(=O)-O-heterocyclyl groups, -C(=O)NH(heterocyclyl) groups,
104 -C(=O)-N(heterocyclyl)₂ groups, -C(=O)-N(alkyl)(heterocyclyl)
105 groups, -C(=O)-N(aryl)(heterocyclyl) groups, substituted and
106 unsubstituted heterocyclylaminoalkyl groups, substituted and
107 unsubstituted diheterocyclylaminoalkyl groups, substituted and
108 unsubstituted (alkyl)(heterocyclyl)aminoalkyl groups, substituted and
109 unsubstituted (aryl)(heterocyclyl)aminoalkyl groups, substituted and
110 unsubstituted hydroxyalkyl groups, substituted and unsubstituted
111 alkoxyalkyl groups, substituted and unsubstituted aryloxyalkyl
112 groups, and substituted and unsubstituted heterocyclyoxyalkyl
113 groups;
- 114 R¹² is selected from the group consisting of H, -OH, alkoxy groups,
115 aryloxy groups, -NH₂, -NH(alkyl) groups, -NH(aryl) groups,
116 -N(alkyl)₂ groups, -N(aryl)₂ groups, -N(alkyl)(aryl) groups,
117 substituted and unsubstituted alkyl groups, substituted and
118 unsubstituted aryl groups, -NH(heterocyclyl) groups,
119 -N(heterocyclyl)₂ groups, -N(alkyl)(heterocyclyl) groups, and
120 -N(aryl)(heterocyclyl) groups;
- 121 R¹⁴ is selected from the group consisting of substituted and
122 unsubstituted alkyl groups, substituted and unsubstituted aryl groups,
123 substituted and unsubstituted heterocyclyl groups, substituted and
124 unsubstituted heterocyclylalkyl groups, -C(=O)H, -C(=O)-alkyl
125 groups, -C(=O)-aryl groups, -C(=O)-heterocyclyl groups,
126 -C(=O)NH₂, -C(=O)NH(alkyl) groups, -C(=O)NH(aryl) groups,

WO 02/18383

PCT/US01/41942

-102-

- 127 -C(=O)N(alkyl)₂ groups, -C(=O)N(aryl)₂ groups,
128 -C(=O)N(alkyl)(aryl) groups, -C(=O)NH-heterocyclyl groups,
129 -C(=O)N-(heterocyclyl)₂ groups, -C(=O)N(alkyl)(heterocyclyl)
130 groups, -C(=O)N(aryl)(heterocyclyl) groups, substituted and
131 unsubstituted aminoalkyl groups, substituted and unsubstituted
132 alkylaminoalkyl groups, substituted and unsubstituted
133 dialkylaminoalkyl groups, substituted and unsubstituted
134 arylaminoalkyl groups, substituted and unsubstituted
135 diarylaminoalkyl groups, substituted and unsubstituted
136 (alkyl)(aryl)aminoalkyl groups, substituted and unsubstituted
137 heterocyclylaminoalkyl groups, substituted and unsubstituted
138 diheterocyclylaminoalkyl groups, substituted and unsubstituted
139 (heterocyclyl)(alkyl)aminoalkyl groups, substituted and unsubstituted
140 (heterocyclyl)(aryl)aminoalkyl groups, substituted and unsubstituted
141 alkoxyalkyl groups, substituted and unsubstituted aryloxyalkyl
142 groups, substituted and unsubstituted hydroxyalkyl groups, and
143 substituted and unsubstituted heterocyclyloxyalkyl groups;
- 144 R¹⁵ is selected from the group consisting of H, substituted and
145 unsubstituted alkyl groups, substituted and unsubstituted aryl groups,
146 and substituted and unsubstituted heterocyclyl groups;
- 147 R¹⁶ is selected from the group consisting of H, substituted and
148 unsubstituted alkyl groups, substituted and unsubstituted aryl groups,
149 substituted and unsubstituted heterocyclyl groups, -C(=O)H,
150 -C(=O)-alkyl groups, -C(=O)-aryl groups, -C(=O)NH₂,
151 -C(=O)NH(alkyl) groups, -C(=O)NH(aryl) groups,
152 -C(=O)N(alkyl)₂ groups, -C(=O)N(aryl)₂ groups,
153 -C(=O)N(alkyl)(aryl) groups, -C(=O)O-alkyl groups,
154 -C(=O)O-aryl groups, substituted and unsubstituted aminoalkyl

WO 02/18383

PCT/US01/41942

-103-

155 groups, substituted and unsubstituted alkylaminoalkyl groups,
156 substituted and unsubstituted dialkylaminoalkyl groups, substituted
157 and unsubstituted arylaminoalkyl groups, substituted and
158 unsubstituted diarylaminoalkyl groups, substituted and unsubstituted
159 (alkyl)(aryl)aminoalkyl groups, substituted and unsubstituted
160 heterocyclalkyl groups, -C(=O)-heterocycl groups,
161 -C(=O)-O-heterocycl groups, -C(=O)NH(heterocycl) groups,
162 -C(=O)-N(heterocycl)₂ groups, -C(=O)-N(alkyl)(heterocycl)
163 groups, -C(=O)-N(aryl)(heterocycl) groups, substituted and
164 unsubstituted heterocyclaminoalkyl groups, substituted and
165 unsubstituted diheterocyclaminoalkyl groups, substituted and
166 unsubstituted (heterocycl)(alkyl)aminoalkyl groups, substituted and
167 unsubstituted (heterocycl)(aryl)aminoalkyl groups, substituted and
168 unsubstituted hydroxyalkyl groups, substituted and unsubstituted
169 alkoxyalkyl groups, substituted and unsubstituted aryloxyalkyl
170 groups, and substituted and unsubstituted heterocycloxyalkyl
171 groups; and

172 R¹⁷, R¹⁹, and R²⁰ may be the same or different and are independently
173 selected from the group consisting of H, -NH₂, -NH(alkyl) groups,
174 -NH(aryl) groups, -N(alkyl)₂ groups, -N(aryl)₂ groups,
175 -N(alkyl)(aryl) groups, -NH(heterocycl) groups,
176 -N(heterocycl)(alkyl) groups, -N(heterocycl)(aryl) groups,
177 -N(heterocycl)₂ groups, substituted and unsubstituted alkyl groups,
178 substituted and unsubstituted aryl groups, -OH, substituted and
179 unsubstituted alkoxy groups, substituted and unsubstituted
180 heterocycl groups, substituted and unsubstituted aryloxy groups,
181 heterocycloxy groups, -NHOH, -N(alkyl)OH groups, -N(aryl)OH
182 groups, -N(alkyl)O-alkyl groups, -N(aryl)O-alkyl groups,
183 -N(alkyl)O-aryl groups, and -N(aryl)O-aryl groups.

WO 02/18383

PCT/US01/41942

-104-

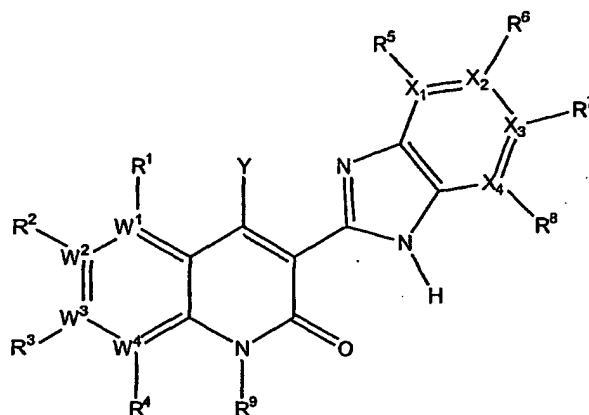
- 1 2. The compound according to claim 1, wherein Y is selected
2 from the group consisting of -OH, -OR⁸ groups, and -NR¹⁰R¹¹ groups.
- 1 3. The compound according to claim 1, wherein Y is a -NR¹⁰R¹¹
2 group.
- 1 4. The compound according to claim 1, wherein Z is an NR¹³
2 group.
- 1 5. The compound according claim 1, wherein R⁴ and R⁷ are
2 hydrogen and R⁵ and R⁶ are selected from the group consisting of hydrogen and
3 alkyl groups having from 1 to 4 carbon atoms.
- 1 6. The compound according to claim 1, wherein R⁵ or R⁶ is an
2 -OR¹⁴ group and R¹⁴ is an alkyl, aryl, heterocyclyl, or heterocyclalkyl group.
- 1 7. The compound according to claim 1, wherein R⁵ or R⁶ is a
2 -OCH₂(CH₂)_q(heterocyclyl) group and q is 0, 1, 2, 3, or 4.
- 1 8. The compound according to claim 1, wherein R¹⁷ is selected
2 from the group consisting of substituted and unsubstituted alkyl groups, substituted
3 and unsubstituted aryl groups, -NH₂, -NH(alkyl) groups, -N(alkyl)₂ groups,
4 -NH(aryl) groups, -N(aryl)₂ groups, -N(alkyl)(aryl) groups, -NH(heterocyclyl)
5 groups, -N(heterocyclyl)(alkyl) groups, -N(heterocyclyl)(aryl) groups,
6 -N(heterocyclyl)₂ groups, and N-containing heterocycles, wherein the N-containing
7 heterocycles are bonded to the carbonyl carbon of the -C(=O)-R¹⁷ group through
8 either a nitrogen atom or a carbon atom in the rings of the N-containing
9 heterocycles.

WO 02/18383

PCT/US01/41942

-105-

- 1 9. A compound having the structure III, a tautomer of the
 2 compound, a pharmaceutically acceptable salt of the compound, or a
 3 pharmaceutically acceptable salt of the tautomer



III

4

5 wherein,

6 W¹, W², W³, and W⁴ are selected from C or N, and at least one of
 7 W¹, W², W³, or W⁴ is N;

8 X¹, X², X³, and X⁴ are selected from C or N, and at least one of X¹,
 9 X², X³, or X⁴ is N;

10 Y is selected from the group consisting of H, -OH, -OR¹⁰ groups,
 11 -SH, -SR¹¹ groups, -NR¹²R¹³ groups, -CN, -C(=O)-R¹⁴ groups,
 12 substituted and unsubstituted alkyl groups, substituted and
 13 unsubstituted alkenyl groups, substituted and unsubstituted alkynyl
 14 groups, substituted and unsubstituted aralkyl groups, substituted and
 15 unsubstituted heterocyclalkyl groups, substituted and unsubstituted
 16 alkylaminoalkyl groups, substituted and unsubstituted
 17 dialkylaminoalkyl groups, substituted and unsubstituted
 18 arylaminoalkyl groups, substituted and unsubstituted

WO 02/18383

PCT/US01/41942

-106-

- 19 diarylaminomethyl groups, substituted and unsubstituted
20 (alkyl)(aryl)aminomethyl groups, substituted and unsubstituted
21 heterocyclylaminoalkyl groups, substituted and unsubstituted
22 diheterocyclylaminoalkyl groups, substituted and unsubstituted
23 (heterocyclyl)(alkyl)aminomethyl groups, substituted and unsubstituted
24 (heterocyclyl)(aryl)aminomethyl groups, substituted and unsubstituted
25 heterocyclyl groups, substituted and unsubstituted aryl groups,
26 substituted and unsubstituted hydroxyalkyl groups, substituted and
27 unsubstituted alkoxyalkyl groups, substituted and unsubstituted
28 aryloxyalkyl groups, and substituted and unsubstituted
29 heterocyclyloxyalkyl groups;
- 30 R¹, R², R³, R⁴, R⁵, R⁶, R⁷, and R⁸ may be the same or different and
31 are independently selected from the group consisting of H, Cl, Br, F,
32 I, -NO₂, -CN, -OH, -OR¹⁵ groups, -NR¹⁶R¹⁷ groups, -C(=O)R¹⁸
33 groups, -SH, -SR¹⁹ groups, -S(=O)R²⁰ groups, S(=O)₂R²¹ groups,
34 substituted and unsubstituted amidinyl groups, substituted and
35 unsubstituted guanidinyl groups, substituted and unsubstituted
36 primary, secondary, and tertiary alkyl groups, substituted and
37 unsubstituted aryl groups, substituted and unsubstituted alkenyl
38 groups, substituted and unsubstituted alkynyl groups, substituted and
39 unsubstituted heterocyclyl groups, substituted and unsubstituted
40 alkylaminomethyl groups, substituted and unsubstituted
41 dialkylaminomethyl groups, substituted and unsubstituted
42 arylaminoalkyl groups, substituted and unsubstituted
43 diarylaminomethyl groups, substituted and unsubstituted
44 (alkyl)(aryl)aminomethyl groups, substituted and unsubstituted
45 heterocyclylalkyl groups, substituted and unsubstituted aminoalkyl
46 groups, substituted and unsubstituted heterocyclylaminoalkyl groups,
47 substituted and unsubstituted diheterocyclylaminoalkyl groups,

WO 02/18383

PCT/US01/41942

-107-

48 substituted and unsubstituted (alkyl)(heterocyclyl)aminoalkyl groups,
49 substituted and unsubstituted (aryl)(heterocyclyl)aminoalkyl groups,
50 substituted and unsubstituted hydroxyalkyl groups, substituted and
51 unsubstituted alkoxyalkyl groups, substituted and unsubstituted
52 aryloxyalkyl groups, and substituted and unsubstituted
53 heterocyclyloxyalkyl groups, and R¹, R², R³, R⁴, R⁵, R⁶, R⁷, and R⁸
54 may be absent;

55 R¹ is absent or H if W¹ is N;

56 R² is absent or H if W² is N;

57 R³ is absent or H if W³ is N;

58 R⁴ is absent or H if W⁴ is N;

59 R⁵ is absent or H if X¹ is N;

60 R⁶ is absent or H if X² is N;

61 R⁷ is absent or H if X³ is N;

62 R⁸ is absent or H if X⁴ is N;

63 R⁹ is selected from the group consisting of H, -OH, substituted and
64 unsubstituted alkoxy groups, substituted and unsubstituted aryloxy
65 groups, -NH₂, substituted and unsubstituted alkylamino groups,
66 substituted and unsubstituted arylamino groups, substituted and
67 unsubstituted dialkylamino groups, substituted and unsubstituted

WO 02/18383

PCT/US01/41942

-108-

68 diarylamino groups, substituted and unsubstituted (alkyl)(aryl)amino
69 groups, substituted and unsubstituted alkyl groups, substituted and
70 unsubstituted aryl groups, -C(=O)H, -C(=O)-alkyl groups, and
71 -C(=O)-aryl groups;

72 R¹⁰ is selected from the group consisting of substituted and
73 unsubstituted alkyl groups, substituted and unsubstituted aryl groups,
74 substituted and unsubstituted heterocyclyl groups, substituted and
75 unsubstituted heterocyclylalkyl groups, -C(=O)H, -C(=O)-alkyl
76 groups, -C(=O)-aryl groups, -C(=O)O-alkyl groups, -C(=O)O-aryl
77 groups, -C(=O)NH₂, -C(=O)NH(alkyl) groups, -C(=O)NH(aryl)
78 groups, -C(=O)N(alkyl)₂ groups, -C(=O)N(aryl)₂ groups,
79 -C(=O)N(alkyl)(aryl) groups, -NH₂, -NH(alkyl) groups, -NH(aryl)
80 groups, -N(alkyl)₂ groups, -N(alkyl)(aryl) groups, -N(aryl)₂ groups,
81 -C(=O)NH(heterocyclyl) groups, -C(=O)N(heterocyclyl)₂ groups,
82 -C(=O)N(alkyl)(heterocyclyl) groups, and
83 -C(=O)N(aryl)(heterocyclyl) groups;

84 R¹¹ and R¹⁹ may be the same or different and are independently
85 selected from the group consisting of substituted and unsubstituted
86 alkyl groups, and substituted and unsubstituted aryl groups;

87 R¹² is selected from the group consisting of H, substituted and
88 unsubstituted alkyl groups, substituted and unsubstituted aryl groups,
89 and substituted and unsubstituted heterocyclyl groups;

90 R¹³ is selected from the group consisting of H, substituted and
91 unsubstituted alkyl groups, substituted and unsubstituted aryl groups,
92 substituted and unsubstituted heterocyclyl groups, -OH, alkoxy
93 groups, aryloxy groups, -NH₂, substituted and unsubstituted

WO 02/18383

PCT/US01/41942

-109-

94 heterocyclylalkyl groups, substituted and unsubstituted aminoalkyl
95 groups, substituted and unsubstituted alkylaminoalkyl groups,
96 substituted and unsubstituted dialkylaminoalkyl groups, substituted
97 and unsubstituted arylaminoalkyl groups, substituted and
98 unsubstituted diarylaminoalkyl groups, substituted and unsubstituted
99 (alkyl)(aryl)aminoalkyl groups, substituted and unsubstituted
100 alkylamino groups, substituted and unsubstituted arylamino groups,
101 substituted and unsubstituted dialkylamino groups, substituted and
102 unsubstituted diarylamino groups, substituted and unsubstituted
103 (alkyl)(aryl)amino groups, -C(=O)H, -C(=O)-alkyl groups,
104 -C(=O)-aryl groups, -C(=O)O-alkyl groups, -C(=O)O-aryl groups,
105 -C(=O)NH₂, -C(=O)NH(alkyl) groups, -C(=O)NH(aryl) groups,
106 -C(=O)N(alkyl)₂ groups, -C(=O)N(aryl)₂ groups,
107 -C(=O)N(alkyl)(aryl) groups, -C(=O)-heterocyclyl groups,
108 -C(=O)-O-heterocyclyl groups, -C(=O)NH(heterocyclyl) groups,
109 -C(=O)-N(heterocyclyl)₂ groups, -C(=O)-N(alkyl)(heterocyclyl)
110 groups, -C(=O)-N(aryl)(heterocyclyl) groups, substituted and
111 unsubstituted heterocyclylaminoalkyl groups, substituted and
112 unsubstituted hydroxyalkyl groups, substituted and unsubstituted
113 alkoxyalkyl groups, substituted and unsubstituted aryloxyalkyl
114 groups, and substituted and unsubstituted heterocyclyloxyalkyl
115 groups;

116 R¹⁴ is selected from the group consisting of H, -OH, alkoxy groups,
117 aryloxy groups, -NH₂, -NH(alkyl) groups, -NH(aryl) groups,
118 -N(alkyl)₂ groups, -N(aryl)₂ groups, -N(alkyl)(aryl) groups,
119 substituted and unsubstituted alkyl groups, substituted and
120 unsubstituted aryl groups, -NH(heterocyclyl) groups,
121 -N(heterocyclyl)₂ groups, -N(alkyl)(heterocyclyl) groups, and
122 -N(aryl)(heterocyclyl) groups;

WO 02/18383

PCT/US01/41942

-110-

- 123 R¹⁵ is selected from the group consisting of substituted and
124 unsubstituted alkyl groups, substituted and unsubstituted aryl groups,
125 substituted and unsubstituted heterocyclyl groups, substituted and
126 unsubstituted heterocyclylalkyl groups, -C(=O)H, -C(=O)-alkyl
127 groups, -C(=O)-aryl groups, -C(=O)-heterocyclyl groups,
128 -C(=O)NH₂, -C(=O)NH(alkyl) groups, -C(=O)NH(aryl) groups,
129 -C(=O)N(alkyl)₂ groups, -C(=O)N(aryl)₂ groups,
130 -C(=O)N(alkyl)(aryl) groups, -C(=O)NH-heterocyclyl groups,
131 -C(=O)N-(heterocyclyl)₂ groups, -C(=O)N(alkyl)(heterocyclyl)
132 groups, -C(=O)N(aryl)(heterocyclyl) groups, substituted and
133 unsubstituted aminoalkyl groups, substituted and unsubstituted
134 alkylaminoalkyl groups, substituted and unsubstituted
135 dialkylaminoalkyl groups, substituted and unsubstituted
136 arylaminoalkyl groups, substituted and unsubstituted
137 diarylaminoalkyl groups, substituted and unsubstituted
138 (alkyl)(aryl)aminoalkyl groups, substituted and unsubstituted
139 heterocyclylaminoalkyl groups, substituted and unsubstituted
140 diheterocyclylaminoalkyl groups, substituted and unsubstituted
141 (heterocyclyl)(alkyl)aminoalkyl groups, substituted and unsubstituted
142 (heterocyclyl)(aryl)aminoalkyl groups, substituted and unsubstituted
143 alkoxyalkyl groups, substituted and unsubstituted aryloxyalkyl
144 groups, substituted and unsubstituted hydroxyalkyl groups, and
145 substituted and unsubstituted heterocycloxyalkyl groups;
- 146 R¹⁶ is selected from the group consisting of H, substituted and
147 unsubstituted alkyl groups, substituted and unsubstituted aryl groups,
148 and substituted and unsubstituted heterocyclyl groups;
- 149 R¹⁷ is selected from the group consisting of H, substituted and
150 unsubstituted alkyl groups, substituted and unsubstituted aryl groups,

WO 02/18383

PCT/US01/41942

-111-

- 151 substituted and unsubstituted heterocyclyl groups, -C(=O)H,
152 -C(=O)-alkyl groups, -C(=O)-aryl groups, -C(=O)NH₂,
153 -C(=O)NH(alkyl) groups, -C(=O)NH(aryl) groups,
154 -C(=O)N(alkyl)₂ groups, -C(=O)N(aryl)₂ groups,
155 -C(=O)N(alkyl)(aryl) groups, -C(=O)O-alkyl groups,
156 -C(=O)O-aryl groups, substituted and unsubstituted aminoalkyl
157 groups, substituted and unsubstituted alkylaminoalkyl groups,
158 substituted and unsubstituted dialkylaminoalkyl groups, substituted
159 and unsubstituted arylaminoalkyl groups, substituted and
160 unsubstituted diarylaminoalkyl groups, substituted and unsubstituted
161 (aryl)(alkyl)aminoalkyl groups, substituted and unsubstituted
162 heterocyclylalkyl groups, -C(=O)-heterocyclyl groups,
163 -C(=O)-O-heterocyclyl groups, -C(=O)NH(heterocyclyl) groups,
164 -C(=O)-N(heterocyclyl)₂ groups, -C(=O)-N(alkyl)(heterocyclyl)
165 groups, -C(=O)-N(aryl)(heterocyclyl) groups, substituted and
166 unsubstituted heterocyclylaminoalkyl groups, substituted and
167 unsubstituted diheterocyclylaminoalkyl groups, substituted and
168 unsubstituted (heterocyclyl)(alkyl)aminoalkyl groups, substituted and
169 unsubstituted (heterocyclyl)(aryl)aminoalkyl groups, substituted and
170 unsubstituted hydroxyalkyl groups, substituted and unsubstituted
171 alkoxyalkyl groups, substituted and unsubstituted aryloxyalkyl
172 groups, and substituted and unsubstituted heterocycloxyalkyl
173 groups; and
- 174 R¹⁸, R²⁰, and R²¹ may be the same or different and are independently
175 selected from the group consisting of H, -NH₂, -NH(alkyl) groups,
176 -NH(aryl) groups, -N(alkyl)₂ groups, -N(aryl)₂ groups,
177 -N(alkyl)(aryl) groups, -NH(heterocyclyl) groups,
178 -N(heterocyclyl)(alkyl) groups, -N(heterocyclyl)(aryl) groups,
179 -N(heterocyclyl)₂ groups, substituted and unsubstituted alkyl groups,

WO 02/18383

PCT/US01/41942

-112-

180 substituted and unsubstituted aryl groups, -OH, substituted and
181 unsubstituted alkoxy groups, substituted and unsubstituted
182 heterocyclyl groups, substituted and unsubstituted aryloxy groups,
183 heterocyclyloxy groups, -NHOH, -N(alkyl)OH groups, -N(aryl)OH
184 groups, -N(alkyl)O-alkyl groups, -N(aryl)O-alkyl groups,
185 -N(alkyl)O-aryl groups, and -N(aryl)O-aryl groups.

1 10. The compound according to claim 9, wherein one of W¹, W²,
2 W³, and W⁴ is N.

1 11. The compound according to claim 9, wherein one of X¹, X²,
2 X³, and X⁴ is N.

1 12. The compound according to claim 9, wherein Y is selected
2 from the group consisting of H, -OH, -OR¹⁰ groups, and -NR¹²R¹³ groups.

1 13. The compound according to claim 9, wherein Y is a -NR¹²R¹³
2 group.

1 14. The compound according to claim 9, wherein R⁵ is H, X⁴ is
2 N, and R⁶ and R⁷ are selected from the group consisting of H and alkyl groups
3 having from one to four carbon atoms.

1 15. The compound according to claim 9, wherein R⁶ or R⁷ is an
2 -OR¹⁵ group and R¹⁵ is an alkyl, aryl, heterocyclyl, or heterocyclylalkyl group.

1 16. The compound according to claim 9, wherein R⁶ or R⁷ is a
2 -OCH₂(CH₂)_q(heterocyclyl) group and q is 0, 1, 2, 3, or 4.

1 17. The compound according to claim 9, wherein R¹⁸ is selected
2 from the group consisting of substituted and unsubstituted alkyl groups, substituted
3 and unsubstituted aryl groups, -NH₂, -NH(alkyl) groups, -N(alkyl)₂ groups,

WO 02/18383

PCT/US01/41942

-113-

4 -NH(aryl) groups, -N(aryl)₂ groups, -N(alkyl)(aryl) groups, -NH(heterocyclyl)
5 groups, -N(heterocyclyl)(alkyl) groups, -N(heterocyclyl)(aryl) groups,
6 -N(heterocyclyl)₂ groups, and N-containing heterocycles, wherein the N-containing
7 heterocycles are bonded to the carbonyl carbon of the -C(=O)-R¹⁸ group through
8 either a nitrogen atom or a carbon atom in the rings of the N-containing
9 heterocycles.

1 18. A pharmaceutical formulation, comprising the compound
2 according to claim 1 in combination with a pharmaceutically acceptable carrier.

1 19. A method of treating a patient in need of an inhibitor of
2 vascular endothelial growth factor receptor tyrosine kinase, comprising
3 administering an effective amount of the pharmaceutical formulation according to
4 claim 18 to a patient in need thereof.

1 20. A pharmaceutical formulation, comprising the compound
2 according to claim 9 in combination with a pharmaceutically acceptable carrier.

1 21. A method of treating a patient in need of an inhibitor of
2 vascular endothelial growth factor receptor tyrosine kinase, comprising
3 administering an effective amount of the pharmaceutical formulation according to
4 claim 20 to a patient in need thereof.

